Doc. Ref.: EMA/60983/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xeplion

International nonproprietary name: paliperidone

Procedure No. EMEA/H/C/2105

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International NV submitted on 3 December 2009 an application for Marketing Authorisation to the Agency for Xeplion, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 November 2008.

The applicant applied for the following indication: Treatment of adult patients with schizophrenia.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/231/2009 on a paediatric investigation plan with a waiver, as modified by the decision P/346/2010 on granting a deferral.

The following conditions are covered in the paediatric investigation plan:

- Schizophrenia
- Schizoaffective disorder

The PIP is not yet completed.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice:

The applicant received Scientific Advices from the CHMP on 27/07/2000, 18/11/2004 and 21/09/2006. The Scientific Advices pertained to non-clinical and clinical aspects.

Licensing status

Xeplion has been given a Marketing Authorisation in the United States on 31 July 2009.

A new application was filed in the following countries: Australia, New Zealand, Canada, Korea, Switzerland, Turkey, Russia, Taiwan, Mexico, Malaysia, Thailand and Singapore.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Tomas Salmonson

Co-Rapporteur: Martina Weise

- The application was received by the EMA on 3 December 2009.
- The procedure started on 23 December 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 March 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 March 2010.
- During the meeting on 22 April 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 April 2010.
- During a meeting of the Scientific Advisory Group (SAG) on 13 July 2010, experts were convened to address questions raised by the CHMP.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 August 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 October 2010.
- During the CHMP meeting on 21 October 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing and oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 12 November 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 29 November 2010.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 10 December 2010.
- During the CHMP meeting on 13 December 2010, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 13-16 December 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Xeplion on 16 December 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 15 December 2010.

2. Scientific discussion

2.1. Introduction

This is a complete, Article 8(3) application for XEPLION (paliperidone) for a known active substance (paliperidone) through the centralised procedure. The product is intended for prescription only.

Paliperidone (9-hydroxy-risperidone) is the major metabolite of risperidone, which is approved for treatment of schizophrenia since 1994. Paliperidone shares the characteristic serotonin (5HT2A) and dopamine (D2) antagonism and receptor binding profile of its parent risperidone. It binds also to a1-adrenergic receptors, and, with lower affinity, to H1-histaminergic and a2-adrenergic receptors, which may explain some of the other effects of paliperidone.

The claimed indication for XEPLION is treatment of adult patients with schizophrenia.

The goals of treatment of schizophrenia are to rapidly eliminate symptoms, reduce the number of relapses, and reduce the severity of the illness. Improving the level of social function and relationships are also important.

Antipsychotics are the mainstay of treatment of schizophrenia. Conventional antipsychotics, typified by haloperidol, have a proven track record over the last half-century in the treatment of schizophrenia. While these drugs are highly effective against the positive, psychotic symptoms of schizophrenia, they show little benefit in alleviating negative symptoms or the cognitive impairment associated with the disease.

Second generation, also called atypical antipsychotics differ considerably in their chemical, pharmacological, and clinical profiles and are generally characterised by effectiveness against both the positive and negative symptoms associated with schizophrenia and with enhanced safety profile with respect to extrapyramidal symptoms.

Although a number of products in this class are currently available, treatment challenges and consequently goals for the development of a new second generation antipsychotic continue to exist such as the need for titration, twice daily dosing, slow onset of action necessitating the use of acute intramuscular treatment, and high treatment discontinuation rates due to lack of compliance or other reasons.

XEPLION (paliperidone palmitate) is a prolonged release aqueous suspension for injection in pre-filled syringes, for intramuscular administration, available in dosage strengths equivalent to 25, 50, 75, 100 and 150 mg paliperidone. Doses of paliperidone palmitate are expressed as mg eq./kg, referring to mg paliperidone (base) equivalents (eq.)/kg body weight (conversion factor paliperidone palmitate to paliperidone, f = 1.56).

XEPLION is intended for once monthly intramuscular (i.m) injection. The recommended dose initiation regimen is 150 mg eq. on Day 1 followed by 100 mg eq. 1 week later, administered in the deltoid muscle in order to rapidly obtain therapeutic plasma concentrations and apparent steady-state, thereby eliminating the need for oral supplementation in the dose initiation phase. The recommended monthly maintenance dosage is once 75 mg eq., which can be administered in the deltoid or gluteal muscle and can be increased or decreased in the range of 25 to 150 mg eq. based on tolerability and/or efficacy in individual patients.

2.2. Quality aspects

2.2.1. Introduction

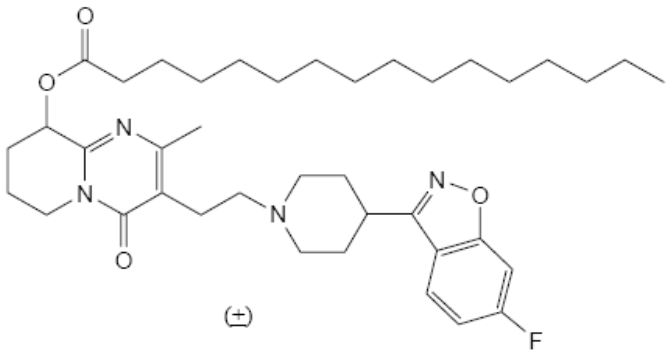
XEPLION is presented as prolonged release suspension for injection containing 25 mg, 50 mg, 75 mg, 100 mg or 150 mg of paliperidone, the active substance, in form of paliperidone palmitate. The suspension is white to off-white and has neutral pH.

Excipients used in the preparation of XEPLION are well known excipients such as polysorbate 20, polyethylene glycol 4000, citric acid, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium hydroxide (for pH adjustment) and water for injections.

The suspension is supplied in pre-filled syringes (cyclic-olefin-copolymer) with a plunger stopper and tip cap (bromobutyl rubber) with a 22G 1½-inch safety needle and a 23G 1-inch safety needle.

2.2.2. Active Substance

Paliperidone palmitate is chemically designated as (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4*H*pyrido[1,2-*a*]pyrimidin-9-yl hexadecanoate, and has the following structure:



Paliperidone palmitate is a white to almost white powder. It is practically insoluble in water or in aqueous buffer over a broad pH range. The molecule contains one chiral center and is synthesised as a racemic mixture. Due to the low solubility in aqueous medium, the partition coefficient P and the ratio of partitioning R could not be determined experimentally.

Paliperidone palmitate exists in a single stable crystalline form designated as form A. Sufficient evidence was provided to prove that the form A is obtained by the utilised manufacturing process.

Manufacture

Sufficient information about manufacturing process of paliperidone palmitate has been provided.

Paliperidone palmitate is manufactured by a five-step process which results in a 'sterile grade' substance. Detailed description of the route of synthesis, including starting materials, has been provided and was considered sufficient. The synthesis involves a carbon treatment followed by a catalytic hydrogenation in the presence of a catalyst which is removed after completion of the reaction. The residue is dissolved and the substance is crystallised. The crystallised paliperidone palmitate is isolated, washed and dried.

A detailed discussion of the critical steps and critical control points for the synthesis was provided. The aseptic manufacturing process was validated. The testing was performed on commercial scale batches in accordance with approved batch records, written procedures, and approved protocols. All acceptance criteria were met.

Confirmation of the chemical structure of paliperidone palmitate was provided by elemental analysis (C, H and N content) and by spectroscopic methods such as UV, IR, ^{1}H-NMR, ^{13}C-NMR as well as by mass spectral analysis. The IR, NMR and MS spectrum assignations were consistent with the declared chemical structure.

In addition the morphology of the substance was studied. Data generated by scanning electron microscopy (SEM) analysis during the screening studies indicated that the drug substance morphology remains identical even when applying a broad range of variables/conditions and using different isolation/drying techniques.

No polymorphs were observed by powder XRD, Raman spectroscopy and DSC. Only one crystalline form has been identified

Potential impurities originating from starting materials, intermediates, by-products, and degradation products have been discussed. The impurity profile of the paliperidone palmitate has been established based on batches used during toxicological evaluation, clinical studies, and drug substance stability studies and produced during validation of the manufacturing process.

The possibility for presence of genotoxic impurities has been investigated. Studies were conducted on some impurities and their derivatives to ensure their removal by the downstream synthesis process to the final "sterile grade" substance.

Specification

The drug substance specification includes tests for physical appearance, identification (IR and HPLC), assay (HPLC), related substances (HPLC), residual solvents (GC), water content (Karl Fisher), residue on ignition, sulphated ash, heavy metals, sterility and bacterial endotoxins.

A detailed description for all analytical methods was provided. Some methods are in accordance with the Ph Eur and their validation was not needed. Complete method validation data was provided for the non compendial (in-house) analytical methods, including IR method for identification and the HPLC method for identification, assay, related substances and the GC method for residual solvents.

The HPLC method has been validated with regard to specificity, linearity, range, limit of quantification (LOQ), limit of detection (LOD), accuracy, precision, robustness, system suitability and stability of solutions. The results indicate that the active substance and its impurities can be determined accurately by this method.

The GC-method used to determine residual solvents has been acceptably validated regarding specificity, accuracy, precision (repeatability), stability of solution, and system suitability. It has been demonstrated that the method was capable of determining several other solvents which are all well separated from the specified residual solvents.

In general specification limits and analytical methods proposed are suitable to control the quality of the drug substance.

Batch analysis results were provided on 48 commercial scale batches. Furthermore, information on batches that were used in nonclinical and clinical studies was also provided. All batches were

manufactured by the proposed commercial manufacturers according in accordance with the proposed process. It can be concluded that the batch analysis results indicate that the process is under control.

Stability

Paliperidone palmitate drug substance has been subject to several stability studies, including stress conditions and studies under long-term (25°C 60%RH), intermediate (35°C 75%RH) and accelerated conditions (40°C 75%RH). The studies were performed on the three registration batches from each of the proposed manufacturers.

In addition forced degradation studies on drug substance in solution were performed. The purpose of this stress study was to identify the main degradation pathway and degradation compounds of the "sterile grade" drug substance and to demonstrate that the HPLC method was stability indicating.

Results generated during the stability program indicated that "sterile grade" paliperidone palmitate was physically and chemically stable during storage at real time, accelerated, and stress conditions. The forced degradation study indicated that all major degradation compounds were separated and no degradation compounds were found to co-elute with the drug substance. It was demonstrated that the HPLC purity method was stability indicating.

It has been confirmed that the first three production-scale batches will be tested according to the protocol. In accordance with EU GMP guidelines [1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim of pharmaceutical development was to obtain a prolonged release formulation of paliperidone with an injection interval of 1 month for the treatment of schizophrenia. It was decided to develop an aqueous suspension of the palmitate ester of paliperidone for intramuscular injection, due to the very low solubility of this ester. Paliperidone palmitate is practically insoluble in aqueous media over a broad pH range. This very low solubility allows formulating a suspension with an extended release profile. A required increase in dissolution rate has been obtained by milling step in order to reduce the particle size of the active substance. The milled paliperidone palmitate particles in the drug product suspension result in a dissolution rate corresponding to an *in-vivo* release of about 1 month.

Different sizes of the suspended particles of the active substance and different compositions of the formulation have been tested and evaluated. Optimization of the formulation focussed on the following criteria:

- a particle size distribution that gives the desired pharmacokinetic profile,
- a suspension that can be easily resuspended,
- a physically and chemically stable formulation,
- a formulation and package that allow for accurate dosing.

Particle size of the active substance can influence the release rate. The release characteristics of the finished product are controlled by two test methods: 1) through *in-vitro* release test and 2) by

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

measuring the particle size distribution of the suspension by means of laser diffraction. The development of both test methods was adequately described and justified.

The manufacturing process has remained equivalent, with regard to process flow and types of equipment, throughout the formulation and process development activities. A robust manufacturing process was developed and characterised via appropriate characterization studies, such as:

- process design studies to evaluate different settings of the milling process parameters,
- process robustness studies to evaluate the impact of input parameters such as the particle size of the active substance,
- product sensitivity studies to evaluate the effect of environmental parameters (light, temperature, oxygen, metal, etc.) on suspension concentrate, PEG 4000/buffer solution, and final bulk suspension.

These studies have led to defining influential and critical process parameters with target settings and proven acceptable ranges and critical control points.

Adventitious agents

No excipients of human or animal origin are used in the manufacturing process of the finished product.

Manufacture of the product

The manufacturing process is sufficiently described as well as a process flow diagram provided. The sterile finished product uses sterile active substance. The in-process controls and critical steps of the manufacturing process have been identified.

Process validation has been performed on three production scale batches. The finished product attributes and in-process controls were monitored for the bulk compounding and filling/stoppering process. The three bulk batches were entirely filled in the six proposed dosage strengths and packaged in the commercial container closure system.

The data shows consistent manufacture and was considered satisfactory. The utilised manufacturing process is sufficiently robust and gives the product of consistent quality, complying with the designed specification.

Product Specification

The drug product specifications include tests for appearance, resuspendability, injectability, identity (IR and HPLC), assay (HPLC), related substances (HPLC), particulate matter, pH, particle size distribution, uniformity of dosage units, *in-vitro* release testing, sterility and bacterial endotoxins.

The proposed specifications at release and shelf life were considered acceptable as they contain all tests required for the proposed dosage form.

Analytical methods have been sufficiently described, some of them are compendial methods described in the Ph Eur. Adequate validation data have been provided for non-compendial methods such as HPLC method for assay of the active substance used for the uniformity of dose units test, HPLC method for assay of used for the in vitro release test, IR method for identification of paliperidone palmitate, HPLC method for assay of the active substance, identity, impurities and degradation products, laser diffraction test method for particle size distribution and sterility test.

Batch analysis data were provided for three production scale batches of the finished product manufactured at the proposed commercial facility according to the manufacturing process. Furthermore, batch analysis data of three stability batches of the finished products manufactured in the pilot manufacturing plant were provided.

Batch analysis results demonstrated compliance with the proposed specification and confirmed consistency and uniformity of the product. The results were consistent from batch to batch and proved that the product can be manufactured reproducibly according to the agreed specifications.

Stability of the product

Stability studies were performed on 3 batches manufactured at the proposed manufacturing site and packed in the container closure system proposed for the commercial product.

Studies were carried out in accordance with current ICH/CHMP guidelines. Stability data submitted covered long-term (25°C 40% RH) intermediate (30°C 35%RH) and accelerated (40°C ≤25% RH) conditions.

Furthermore the applicant has committed to place one batch upon scale-up on stability. Also at least one production scale batch per year packaged in the commercial packaging system will be placed on long-term stability.

The available stability data demonstrated that the drug product, stored in prefilled syringes, had acceptable stability behaviour. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Sufficient information about the active substance, paliperidone palmitate, has been provided.

The drug substance has been satisfactorily characterised. The synthesis process has been well developed and is well controlled.

Known and potential impurities have been satisfactorily addressed. The control tests and specifications for drug substance product are in line with the requirements of ICH Q6A and Ph Eur requirements for substances for pharmaceutical use and considered satisfactory.

A retest period was supported by satisfactory stability studies.

The finished product is a prolonged release suspension for injection containing 25 mg, 50 mg, 75 mg, 100 mg or 150 mg of paliperidone, the active substance, in form of paliperidone palmitate. The composition of the finished product has been described, and all excipients have been fully characterised.

The development pharmaceutics has been satisfactorily described. The formulation development focused on achieving an extended release formulation of paliperidone with an injection interval of 1 month for the treatment of schizophrenia. Particle characteristics of the drug substance which may affect the rate of release of the active substance have been comprehensively investigated. The final formulation has been selected based on several formulation and optimization studies.

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

The manufacturing process uses aseptic milling to reduce the particle size of the drug substance. Critical steps in the manufacture were identified and adequate in-process control and testing procedures were established. Process validation has been performed on three production scale batches.

The proposed specifications include all tests relevant to this dosage form and the limits are generally acceptable. All analytical procedures and test methods have been adequately described and validated. The batch data demonstrate consistent manufacture.

The stability programme is considered satisfactory. The batches placed on stability are considered representative of the product to be marketed. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The drug substance and the drug product have been appropriately characterised and generally satisfactory documentation has been provided. The results indicate that the drug substance and the drug product can be reproducibly manufactured and therefore the product should have a satisfactory and uniform performance in the clinic.

2.3. Non-clinical aspects

Pivotal toxicology studies were performed according to Good Laboratory Practices (GLP), as stated by the applicant.

2.3.1. Introduction

Following i.m. injection, the paliperidone palmitate pro-drug is hydrolysed to its active compound paliperidone. The systemic exposure to paliperidone palmitate was found to be very low in humans and was measured at levels below or marginally higher than the lower limit of quantification. Consequently, systemic effects are predominantly mediated through paliperidone. Paliperidone palmitate is thus expected to exhibit the same pharmacological properties as paliperidone as described below. No specific pharmacology studies in animal models for paliperidone palmitate have been conducted.

2.3.2. Pharmacology

Paliperidone (R076477 or 9-OH-risperidone) is a receptor monoaminergic antagonist that exhibits the characteristic dopamine type 2 (D2) and serotonin (5-hydroxytryptamine [5-HT] type 2A [5-HT2A]) antagonism of antipsychotic drugs. Paliperidone is the major active metabolite of risperidone which is a widely used atypical antipsychotic approved for the treatment of schizophrenia and other psychiatric disorders.

The binding profiles for paliperidone, its enantiomers R078543(+) and R078544(−) and risperidone are comparable. Paliperidone is also an antagonist at α1- and α2-adrenergic receptors and the histamine H1-receptor in vitro and in vivo.

Primary pharmacodynamic studies

Paliperidone displays high affinity for 5-HT2A (Ki 0.22-0.25 nM) and D2 (Ki 4.6 nM) receptors, and is also active as an antagonist at the α1-and α2-adrenergic receptors and the H1-receptor. Binding

affinities and profiles for all investigated receptor sites are similar for paliperidone, its enantiomers and risperidone. Several in vivo studies were performed in rats and dogs. In rats, paliperidone was slightly less potent than risperidone at early time intervals, but became equipotent at later time intervals, probably reflecting a slower rate of brain penetration. In dogs, paliperidone, its enantiomers and risperidone were roughly equipotent against apomorphine-induced emesis.

Overall, paliperidone induced the expected effects (activity in functional pharmacology models) and the investigated in vivo effects were qualitatively and quantitatively similar for paliperidone and risperidone.

Secondary pharmacodynamic studies

Dopamine secreted in the portal hypophyseal circulation inhibits prolactin release. By antagonizing this tonic inhibitory action of endogenous dopamine, D2 receptor antagonists elevate prolactin release. The suppressive effect of dopamine on prolactin release in rat anterior pituitary cells was dose-dependently antagonized by paliperidone, risperidone and haloperidol. Both paliperidone and risperidone were less potent than haloperidol in this in vitro assay, (2 and 3 times less potent, respectively). Paliperidone was equipotent to risperidone in reversing the dopamine-induced suppression of prolactin release from anterior pituitary cells. Both compounds provoked more pronounced plasma prolactin levels than haloperidol when measured 1 h after identical i.p. or oral doses.

Overall, secondary pharmacodynamic effects and side effect (pre-clinical) profile of paliperidone are very similar to those of risperidone. Anti-adrenergic and anti-histaminergic effects are suspected to elicit hypotensive and sedative effects. Hyperprolactinemia is expected due to the D2-receptor antagonism.

Safety pharmacology programme

In in-vitro studies paliperidone at concentrations of > 1 µM inhibited both HERG currents and native membrane potassium current (IKr), prolonged the action potential duration (APD), occasionally induced early after depolarisation (EADs), instability, triangulation and Torsade de Pointes (TdP) arrhythmias, which are all markers for a torsadogenic potential. Therefore, the slight inhibitory effects of paliperidone on both inward rectifier potassium (Ina) and L type calcium current (ICa,L), which were observed at a concentration of 10 µM, did not seem to be protective against the induction of TdP arrhythmias by paliperidone at micromolar concentrations. Therapeutically effective free plasma concentrations of paliperidone in humans are about 20 nM. A 30-fold margin between free therapeutic plasma concentrations and half maximum inhibitory concentration (IC50) values for the block of HERG currents appears to be a line of demarcation between the majority of drugs associated with TdP arrhythmias and those which are not. Therefore, when the paliperidone concentrations effective in in-vitro electrophysiological studies are compared to therapeutically effective free plasma concentrations, paliperidone seems to have a low torsadogenic potential.

In-vivo studies performed in guinea-pigs and dogs did not show marked effects of paliperidone on QTc at micromolar plasma concentrations, which might question the relevance of these in-vivo models. However, in the Carlsson model, paliperidone did demonstrate effects on the QTc.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were carried out with paliperidone palmitate, pro-drug of paliperidone. The CHMP considered this acceptable since there is an extensive clinical and non clinical

experience with risperidone and also taking into account that administration of risperidone results in significant paliperidone exposure.

2.3.3. Pharmacokinetics

Pharmacokinetic profile of paliperidone palmitate was studied to specifically characterise the absorption and distribution of the product using different formulations and several species (dogs, rats, minipigs and pigs). Given the systemic exposure to paliperidone palmitate is low (due to extensive hydrolysis into paliperidone and palmitic acid), no ex vivo induction and inhibition studies, or in vivo metabolism studies were performed. Furthermore, no studies on plasma protein binding and distribution to blood cells were conducted, nor excretion studies or studies on placental transfer. Available studies are derived from oral paliperidone and/or risperidone.

Paliperidone showed a high bioavailability after i.m dosing of paliperidone palmitate. The shape of the pharmacokinetic profile of paliperidone after intramuscular or intralipomatous administration was similar, but paliperidone plasma concentrations after intralipomatous dosing were on average 28% lower as compared to intramuscular administration. An intravenous administration of paliperidone palmitate, did not produce an immediate release of paliperidone, but resulted in measurable paliperidone plasma concentrations for a period of 9-41 days. Maximum plasma concentrations were reached within one to two weeks across species. Elimination half-lives appeared to be similar between rats and dogs (3-6 and 2-4 days, respectively) but longer in pigs and minipigs (7-15 days). Although the relative bioavailability over the dosing interval of 1 month was highly variable among species and tested formulations, the overall paliperidone palmitate pro-drug exposure was low.

Two in vitro studies investigated the hydrolysis of paliperidone palmitate to paliperidone and palmitic acid. Hydrolysis can take place in several matrices and appeared to be highest in liver samples and occurring to a lower extent in muscle tissue and blood. Based on inhibition studies, serine esterases seemed to be involved in the hydrolysis of paliperidone palmitate, but other esterases may also contribute. Since in vitro results indicated that paliperidone palmitate can be hydrolysed in several matrices and by several esterases, the hydrolysis capacity in vivo is expected to be high. In the carcinogenicity study in rat, the fraction of paliperidone palmitate in plasma was maximally 2.9 to 6.7% of the paliperidone AUC. There was a stereoselectivity in hydrolysis of the ester favouring more towards release of the R078543(+) –enantiomer.

In a quantitative whole body autoradiography in rats, an agglomerate of paliperidone palmitate nanoparticles was formed in the muscle after intramuscular injection. This agglomerate functioned as the depot from where the drug substance was released. High levels of ^{14}C-labelled paliperidone and its metabolites were found in intestinal and urinary contents and distributed extensively in a declining order to the following organs: salivary glands > prostate and liver > kidney, spleen and adrenal glands.

After 6 months of dosing in dogs, highest tissue to plasma (T/P) ratios of paliperidone were found in the lymph nodes (= 119) and in muscle at the injection site (up to 91). Lower T/P ratios between 4.8 and 9.5 were determined for liver, lung and kidney, whereas concentration in brain and non-injected muscle was equivalent to plasma. After 12 months, highest concentrations of paliperidone were found in muscle at the injection site (mean T/P-ratio= 78) compared to lower levels in kidney, lymph nodes, lung and liver (mean T/P-ratio = 6). Concentrations in brain and in non-injected muscle were similar or lower than in plasma.

After single dosing in minipigs, T/P-ratios of paliperidone in the injection site muscle ranged from 71 to 489 between 1 week and 5 months after administration.

In plasma protein binding studies it was shown that in all species tested, including human, paliperidone was bound to a maximum of 85 %. Plasma protein binding of the enantiomers exhibited species-dependent stereoselectivity, with higher protein binding seen with R078543(+) than with R078544(-) in dog and human plasma. In human plasma, paliperidone was predominantely bound to the α1-acid glycoprotein.

Paliperidone crossed the blood-brain barrier. Available data with risperidone indicated that placental transfer was limited in rats. In addition, Paliperidone and/or its metabolites were excreted into milk in rats.

In rats, paliperidone was extensively metabolized and the excretion of unchanged paliperidone accounted for 3.19 (male) and 6.42% (female) of the dose. The urine and faeces obtained from rats contained unchanged paliperidone and seven metabolites, M1, M6, M7, M8, M9, M10, M11, (each accounting for more than 1% of the dose), and four minor metabolites (each accounting for less than 1% of the dose). In rat plasma, paliperidone was the major compound (50-68%). In rats, paliperidone was mostly metabolized by alicyclic hydroxylation, oxidative N-dealkylation and benzisoxazole scission.

In dogs, the excretion of total radioactivity in urine and faeces were slower than in the rat: at 168 hours after dosing, 59.8% the dose was excreted in urine and 32.4% of the dose was excreted in faeces. Metabolism was limited and after 48 hours the unchanged paliperidone accounted for 32.4% in the urine and none in faeces. The urine and faeces obtained from dogs contained also five metabolites, M8, M9, M10, M11, M12, M16 (accounting each for 1.2-6.5% of the total radioactivity). Unchanged paliperidone accounted for 82% of the total radioactivity in plasma (0-24h sample). In dog plasma only paliperidone and the M9 metabolite were detected (M9 accounting for up to 5% of plasma total radioactivity). In the excreta of dogs, biotransformation products resulted from oxidative N-dealkylation, alcohol dehydrogenation and benzisoxazole scission, whether or not in combination with glucuronidation, alicyclic mono-hydroxylation or di-hydroxylation.

In vitro results revealed the possible involvement of CYP3A4 and CYP2D6 in the overall metabolism of paliperidone, and in the formation of M11via benzisoxazole scission. No ex vivo induction and inhibition studies have been performed. However, the effect of risperidone on hepatic enzyme activity was examined in an ex vivo study, in which male Wistar rats were administered risperidone as repeated daily p.o. doses for 1 week. Risperidone exhibited no effects in vivo on any of the cytochrome P450 isoenzyme activities measured, or on UDP-glucuronosyltransferase activity. In vitro studies with Caco-2 cells indicated that paliperidone appears to have a weak P-gp inhibitory effect. No in vivo studies were performed and the clinical relevance is unknown.

In rats, most of the paliperidone-related radioactivity (86%) was excreted with the faeces. In dogs and humans, the most important excretion route was urine. In humans the cumulative excretion in the urine amounted to 79.6% of the dose.

2.3.4. Toxicology

The following toxicology studies were performed with different paliperidone palmitate drug product formulations (F001, F004, F007, F008, F009, F010, F011 and F013): 1) single-dose toxicity studies in dogs, pigs and minipigs, 2) repeat-dose toxicity studies up to 6 months in rats, 12 months in dogs, and 3 months in minipigs 3) in vitro genotoxicity studies, 4) a rat carcinogenicity study and 5) a rat embryo-fetal developmental toxicity study. The single- and repeat-dose toxicity studies (including the carcinogenicity study) addressed both systemic toxicity and local tolerance.

F011 and F013 formulations are considered in principle similar and F013 is the formulation intended to be marketed (see section 3.4.2).

Single dose toxicity

Following single i.m. injection of paliperidone palmitate (F013) in minipigs (dose up to 20 mg eg/kg), dose-dependent granulomatous inflammation was observed in the injected muscle of all animals, which was rated massive on days 8 and 29 after administration. At the same time points, minimal to slight muscular necrosis and concomitant regeneration were noted. These changes decreased over time. Regeneration was also detected in the vehicle group. In dogs, most notable findings were anaphylactic reactions and more pronounced injection site reactions. Signs of CNS toxicity (e.g sedation, tremors, abnormal behaviour) were observed in all animal species.

Repeat dose toxicity

Studies were performed in rats (up to 6 months and 160 mg eq./kg), dogs (up to 12 months and 80/40 mg eq./kg) and minipigs (up to 3 months and 20 mg eq./kg). Toxicity findings were mainly related to exaggerated pharmacology, particularly due to dopamine D2 antagonism. Treatment-related sedation and ptosis were consistently observed in all species. In addition, enhanced prolactin release was associated with changes in the pituitary gland, mammary gland, endocrine pancreas, female genital tract, male accessory sex organs and adrenal glands. Changes in body weight, body weight gain and food consumption were also noted. Treatment related changes due to anti-adrenergic activity were also seen as an increased accumulation of red blood cells in the red pulp of the spleen.

Furthermore, toxicity at the injection site was observed. These lesions occurred at all dose levels and across all animal species tested with tendency to be dose dependent. The most sensitive species was the dog. Across all tested species independent of the formulation (F004, F011) inflammatory reactions were observed in the repeat-dose toxicity studies with focal necrosis in the 6- and 12-month dog and in the 6-month rat study. Abscess formation occurred in the 6- and 12-month dog studies and was also found in the rat carcinogenicity study. The lowest dose (5 mg eq./kg) and the smallest injection volume (0.05 ml/kg), where abscesses and/or focal necrosis were seen in dogs, exceeded the maximum recommended human dose (MRHD, approximately 2.5 mg eq./kg) and the maximum recommended injection volume (approximately 0.025 ml/kg) in 60 kg patients of 2-fold.

In the 3 month minipig study, in which the formulation intended for marketing (F013) has been tested a dose-related local reaction was found at the injection site after repeated dosing of approximately 5 and 20 mg eq./kg/month. Deposit of test article formulation was observed in the subcutaneous tissue and/or fat, and/or the injection site muscle. Histologically a dose-related (fibro) histiocytic inflammatory reaction, often with granuloma formation especially in the high-dose group, was found . Since injection site lesions occurred at all dose levels, No observed adverse effect levels (NOAEL) could not be established. Altogether, the toxicity studies consistently demonstrated a pronounced irritation potential of aqueous suspensions of paliperidone palmitate at the injection site across all animal species tested.

Genotoxicity

Paliperidone palmitate was not genotoxic in the Ames bacterial gene mutation test and in the mouse lymphoma assay. No specific in vivo genotoxicity test has been performed with paliperidone palmitate which was considered acceptable taking into account that oral paliperidone showed no genotoxic potential in the rat micronucleus test.

Carcinogenicity

The carcinogenic potential of paliperidone palmitate was assessed in a 24-month study in rats following intramuscular administration at doses of 10, 30 or 60 mg eq./kg/month. Pituitary hyperplasia was reported resulting in hyperprolactinemia-related non-neoplastic changes in the mammary gland, and male and female genital tract. Mammary gland adenocarcinomas were observed in the female rats at all dose levels. At 30 and 60 mg eq./kg/month, the incidence of mammary gland adenoma/carcinoma was increased also in male rats. All these findings were expected and in accordance with those seen in the dietary carcinogenicity studies in mice and rats using risperidone with dosages of 0, 0.63, 2.5, or 10 mg/kg bw/day. At the injection site, a deposit was found at all dose levels and abscesses were additionally seen in a few high dose animals.

Reproduction Toxicity

No specific fertility and early embryonic developmental, pre- and postnatal developmental toxicity studies or juvenile animal studies were conducted with paliperidone palmitate to the exception of an embryo-foetal toxicity study performed with intramuscular paliperidone palmitate with doses up to 160 mg eq./kg. This was considered acceptable taking into account that these studies were performed for oral paliperidone and risperidone. Both of these compounds had no influences on male fertility up to 2.5 mg/kg/day in rats. Higher dosages were impeded by the prolactin-mediated decreases in mating behaviour and copulation rate. In female rats, hyperprolactinaemia prolonged oestrus cycles resulted in pseudopregnancies and an elongation of pre-coital intervals. Moreover, pre-implantation losses were increased at the maternally toxic top dose level of 2.5 mg/kg/day.

No foetotoxicity or malformations were observed following i.m. injection of paliperidone palmitate in pregnant rats and similar findings were observed with risperidone or oral paliperidone even at maternally toxic dose levels (up to 10 mg/kg/day). In rabbits, maternal toxicity was found at doses $\geq$ 1.25 mg/kg/day for risperidone or paliperidone culminating in post-implantation losses and foetal death at 5 mg/kg/day.

Both risperidone and oral paliperidone did not reveal any teratogenic potential in rats and rabbits. A decrease in survival of rat pups was observed only at the maternally toxic dose of 2.5 mg/kg/day or higher. At lower dosages, no adverse effects on growth or reproductive performance of the offspring were detected. In juvenile rats treated orally from day 12 to day 50 of age (equivalent to a human paediatric population of 5 to 16 years of age) with up to 1.25 mg/kg/day of risperidone, sexual maturation was not affected. However, body weight gain, motor-coordination, activity as well as learning and memory were impaired. Apart from the latter finding in males, these events were reversible. When juvenile rats were administered with p.o. paliperidone from days 24 to 73 of age (corresponding to adolescents of 12 to 17 years of age), effects on learning and memory were only determined in females of the 2.5 mg/kg/day high dose group, whereas no adverse findings were noted in males or at lower doses. In juvenile dogs treated orally risperidone for 40 weeks commencing just after weaning, sexual maturity was delayed consequent to reduced testosterone and progesterone levels but was in progress during the 12 months recovery period, the NOAEL was therefore set at 1.25 mg/kg/day.

Toxicokinetic data

Toxicokinetic data were collected from the toxicology, carcinogenicity and reproductive toxicity studies specifically conducted with paliperidone palmitate.

In rats, two C_{max}-values were observed. The first peak occurred within 24 h after dosing, then plasma concentrations declined until one or two days after dosing. Thereafter, the plasma concentrations gradually increased towards a second C_{max}, peaking within one week after the first administration. Finally, paliperidone plasma levels slowly declined until the next injection. The AUC-values increased approximately dose- proportionally. In the carcinogenicity study in rats, the maximum plasma concentrations of paliperidone were observed on Day 7 post-dose. AUC- and Cmax-values increased approximately dose-proportionally and were higher in females than in males.

In dogs, plasma concentrations increased until 7 or 14 days after dosing. Thereafter they remained approximately stable until 3 or 4 weeks post-dose. Cmax- and AUC0- 21 days-values appeared to increase dose proportionally in the dosing interval.

Local Tolerance

The single- and repeat-dose toxicity studies (including the carcinogenicity study) addressed local tolerance (see above).

Other toxicity studies

No other toxicity studies were specifically performed with paliperidone palmitate. Available studies derived from oral paliperidone and/or risperidone.

No immunotoxicity was evident in repeated-dose toxicity studies with either risperidone or oral paliperidone. Furthermore, no effect of paliperidone treatment on primary T-cell-dependent antibody response was found in a specific study conducted in immunised rats. Anaphylactic-like reactions seen in repeated-dose toxicity studies with paliperidone palmitate were considered dog-specific response to polysorbate 20.

No antigenicity studies have been performed with either oral paliperidone or the paliperidone palmitate in the light of the non-peptidogenic nature of the compounds and the absence of immunotoxicity upon repetitive dosing in toxicity studies.

In an in vitro phototoxicity study, paliperidone had previously been shown to be devoid of any phototoxic potential in mouse 3T3 cells in the presence of UV light. In addition, paliperidone did not reveal any photo-mutagenic activity in an Ames test using the S. typhimurium tester strains TA98, TA1537, TA100 and TA1535 (DNA repair-deficient strains) and in the TA102 strain (DNA repair-proficient strain), paliperidone did not induce any photo mutagenic activity. A positive effect was only observed in the tryptophan-requiring and DNA repair-deficient bacterial strain E. coli WP2 uvrA which was attributed to a "feeding effect" (increase in reversion rates in the absence of a mutational event caused by photo-excitation that lead to tryptophan biosynthesis in auxotroph E. coli WP2 uvrA bacteria).

The structurally-related impurities R206474, R206475, R207919, R208224 and R208225 have been adequately qualified. The two genotoxic impurities T002006 and T002026 and the oxidative degradants formaldehyde and acetaldehyde were also satisfactorily specified.

2.3.5. Ecotoxicity/environmental risk assessment

An ERA according to CHMP guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00, June 2006) and available studies are derived from oral paliperidone. Based on estimated sale forecast for 2016 in the European Union, the total Predicted Environmental Concentration in surface water $PEC_{SURFACE\ WATER}$ was 0.0027 µg/L (<0.01 µg/L) for

paliperidone and paliperidone palmitate, so no further testing was required and no additional impact to the environment is expected with the use of paliperidone palmitate.

2.3.6. Discussion on non-clinical aspects

No pharmacological studies were specifically conducted with paliperidone palmitate in animals. Paliperidone palmitate is hydrolysed into paliperidone and palmitic acid and is thus expected to exhibit the same pharmacological properties as paliperidone. Paliperidone is the major active metabolite of the atypical neuroleptic risperidone. It is a racemic substance that exists in two configurations. Interconversion of the enantiomers occurs extensively *in vivo*, favouring the (+)-conformation. Therefore, primary and secondary pharmacodynamic studies were in part performed with the racemate and the individual enantiomers and have been compared to the pharmacodynamics of risperidone. Pharmacodynamic profiles were very similar for all compounds, both qualitatively and quantitatively with prominent antagonism at serotonin 5-HT_{2A}- and dopamine D_2-receptors. Secondary pharmacodynamic effects of the compounds were related to anti-adrenergic and anti-histaminic activity and to hyperprolactinaemia elicited by D_2-receptor antagonism. Side effects of paliperidone closely resemble to those of risperidone. Hence cardiac effects (e.g torsade de pointes, arrhythmias) were reflected in the product information for XEPLION including a warning in patients using other medications known to prolong the QT interval.

The results of pharmacokinetic studies in animals showed that the systemic exposure to paliperidone palmitate is low due to high hydrolysis into paliperidone and palmitic acid. Hence the majority of the pharmacokinetic profile for paliperidone palmitate has already been characterised with oral paliperidone and/or risperidone (crossed the blood brain barrier, limited placental transfer, maximum of 85% plasma protein binding; excretion into faeces, urine and notably milk). Paliperidone showed a high bioavailability after i.m dosing of paliperidone palmitate. The shape of the pharmacokinetic profile of paliperidone after intramuscular or intralipomatous administration was similar, but paliperidone plasma concentrations after intralipomatous dosing were on average 28% lower as compared to intramuscular administration. An intravenous administration of paliperidone palmitate, did not produce an immediate release of paliperidone, but resulted in measurable paliperidone plasma concentrations for a period of 9-41 days. High tissue distribution (forming anagglomerate) was observed in the muscle at the injection sites in all studied species.

The majority of the findings in the repeated dose toxicity studies with paliperidone palmitate were related to the exaggerated pharmacological activity of paliperidone, particularly due to dopamine D2 antagonism. Treatment-related sedation and ptosis were consistently observed in all species. In addition, enhanced prolactin release was associated with changes in the pituitary gland, mammary gland, endocrine pancreas, female genital tract, male accessory sex organs and adrenal glands. Changes in body weight, body weight gain and food consumption were also noted. Treatment related changes due to anti-adrenergic activity were also seen as an increased accumulation of red blood cells in the red pulp of the spleen.

Toxicity at the injection site was also observed. Since injection site lesions occurred at all dose levels, NOAELs could not be established. Altogether, the toxicity studies consistently demonstrated a pronounced irritation potential of aqueous suspensions of paliperidone palmitate at the injection site across all animal species tested. The issue is further discussed under the clinical aspects (see section 3.4). Furthermore, anaphylactic-like reactions seen in repeated-dose toxicity studies with paliperidone palmitate were considered dog-specific response to polysorbate 20.

In the carcinogenicity study specifically conducted with paliperidone palmitate, a significant increase in mammary gland adenocarcinomas in female rats at 10, 30 and 60 mg/kg/month was observed. Male

rats showed a significant increase in mammary gland adenomas and carcinomas at 30 and 60 mg /kg/month. These tumours can be related to prolonged dopamine D2 antagonism and hyperprolactinemia. All these findings were expected and in accordance with those seen in the dietary carcinogenicity studies in mice and rats using risperidone with dosages of 0, 0.63, 2.5, or 10 mg/kg bw/day. The relevance of these tumour findings in rodents in terms of human risk is considered unknown.

There was no evidence of genotoxic potential with paliperidone palmitate. This finding was further supported by in vivo genotoxic study performed with oral paliperidone.

No foetotoxicity or malformations were observed following i.m. injection of paliperidone palmitate in pregnant rats and similar findings were observed with risperidone or oral paliperidone even at maternally toxic dose levels (up to 10 mg/kg/day). In rabbits, maternal toxicity was found at doses ≥ 1.25 mg/kg/day for risperidone or paliperidone culminating in post-implantation losses and foetal death at 5 mg/kg/day.

Both risperidone and oral paliperidone did not reveal any teratogenic potential in rats and rabbits and no specific study was conducted with paliperidone palmitate in this regard.

Based on estimated sale forecast for 2016 in the European Union, the total Predicted Environmental Concentration in surface water $PEC_{SURFACE\ WATER}$ was <0.01 µg/L for paliperidone and paliperidone palmitate, and no additional impact to the environment is expected with the use of paliperidone palmitate.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical aspects of paliperidone palmitate have been adequately documented and meet the requirements to support this application.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

However, some GCP and/or protocol compliance deficiencies were encountered in the following clinical phase II/III studies: SCH-201, PSY-3003 and PSY-3002. GCP issues led to the closure of 2 sites in both studies PSY-3001 and -3002 and included errors occurring with the Interactive Voice Response System (IVRS). On the basis of sensitivity analyses performed by the applicant, the CHMP concluded that these data could be used for the evaluation of the present application.

2.4.2. Pharmacokinetics

The Phase I clinical pharmacology program has been conducted in patients with schizophrenia using different paliperidone palmitate product drug formulations.

In addition to the Phase I studies, pharmacokinetics data have been collected from the Phase III studies for population pharmacokinetic analysis. An *in vitro-in vivo* correlation (IVIVC) study for paliperidone palmitate was also performed. Finally, pharmacokinetic characteristics derived from studies with oral paliperidone, were also considered.

Plasma concentration of papliperidone palmitate, paliperidone and analysed metabolites was determined firstly using radioimmunassay (RIA) and thereafter LC/MS/MS methods in the pharmacokinetic (PK) studies. Pharmacokinetic parameters were determined using non compartmental models. IVIC and Population PK analysis were conducted using nonlinear mixed effects modeling methodology (NONMEM).

Absorption

Bioavailability

Following a single im dose of paliperidone palmitate, plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median tmax of 14 days (12-16 days). The release of the drug starts as early as Day 1, and the apparent half-life for paliperidone following i.m. injection of paliperidone palmitate is approximately 25 days for a dose of 25 mg eq., 30 days for a dose of 50 mg eq., 44 days/40 days (deltoid/gluteal) for a dose of 100 mg eq., and 40 days/49 days (deltoid/gluteal) for a dose of 150 mg eq.

The absolute bioavailability of paliperidone using i.m. administration of paliperidone palmitate was estimated to be complete based on the comparison between i.m. routes of paliperidone palmitate and immediate release (IR) paliperidone. Relative bioavailability of paliperidone palmitate compared to intramuscularly administered IR paliperidone ranged from 57% to 135%, depending on the tested formulations. A direct comparison with i.v. paliperidone has not been performed and was not considered necessary.

An effect of the particle size on the release rate was observed suggesting a slower release rate when the particle sizes were increased (decreased median Cmax , increased median tmax).

Relative bioavailability of the formulations used in Phase III studies, F011 and F013 (intended to be marketed) showed that point estimates for AUC and Cmax were close to 100%. However the 90% confidence intervals did not fall within acceptable limits to demonstrate bioequivalence.

A Level A IVIVC model has been established for paliperidone palmitate, confirming the biological relevance of the in vitro dissolution method and that this model can be further used to justify bio relevant release rate specifications for formulation intended to be marketed (F013).

Effect of injection site (deltoid versus gluteal muscle)

Initiation of treatment in the deltoid muscle resulted in higher initial exposure as compared to initiation of treatment in the gluteal muscle, suggesting more rapid achievement of therapeutic concentration. This is likely explained by the different distribution of muscle and adipose tissue between the two injection sites, which may affect the uptake of paliperidone in the circulation at the site of injection. The effect seemed greater at initiation of treatment, while after multiple injections, the fluctuations in paliperidone plasma concentrations were less pronounced, and a difference between deltoid and gluteal injections were less apparent.

Effect of injection volume

After single im administration of paliperidone palmitate at different doses, apparent half-life of paliperidone was estimated to be longer at the higher doses compared with the lower doses, reflecting a slower absorption. This may be caused by the increased injection volume from 0.25 to 1.5 mL over the dosing range of 25 to 150 mg eq.

Effect of body mass index (BMI)

At initiation of treatment, a 21% to 32% lower exposure on Days 8 and 15 in the overweight and obese groups was observed as compared to the normal BMI group. After the 8th and 14th injections, there was no major difference in AUC_T or Cmax between the normal BMI and overweight groups and some difference compared with the obese subjects.

Comparison of exposure with oral paliperidone

No direct comparison of plasma concentrations between oral paliperidone (Invega) and the proposed dose regimen for paliperidone palmitate has been performed. However, pharmacokinetic data from study SCH-201 were presented. Study SCH-201 included an open label oral dosing regimen (6 mg or 12 mg Invega , 2 mg or 4mg immediate release oral paliperidone once daily for 7 days) and thereafter compared 2 fixed doses of paliperidone palmitate (50 mg and 100 mg eq) versus placebo administered at day 1,8 and 36. Based on dose-normalised comparisons, comparable exposure for Invega 6 mg/day (recommended dose) and paliperidone palmitate 75 mg eq./month (recommended monthly maintenance dose) was observed with an 8% higher estimated exposure with paliperidone palmitate versus Invega. In addition, simulations based on PK population analyses were further discussed by the applicant. In these simulations, plasma concentrations of paliperidone after administration of 150 mg eq. paliperidone palmitate on day 1 are slightly below the concentrations after administration of Invega 6 mg/day during the first days, but 4-5 days after administration the concentrations were very similar.

Figure 1. Simulated Paliperidone Concentration-Time Profiles for the First Week of Treatment for Paliperidone PR vs. Paliperidone Palmitate Recommended Loading Dose Injection on Day 1. The white and black lines represent plasma paliperidone concentrations after administration of Paliperidone PR and Paliperidone Palmitate respectively. The shaded and hatched areas represent the 90% prediction interval based on the population PK simulation.

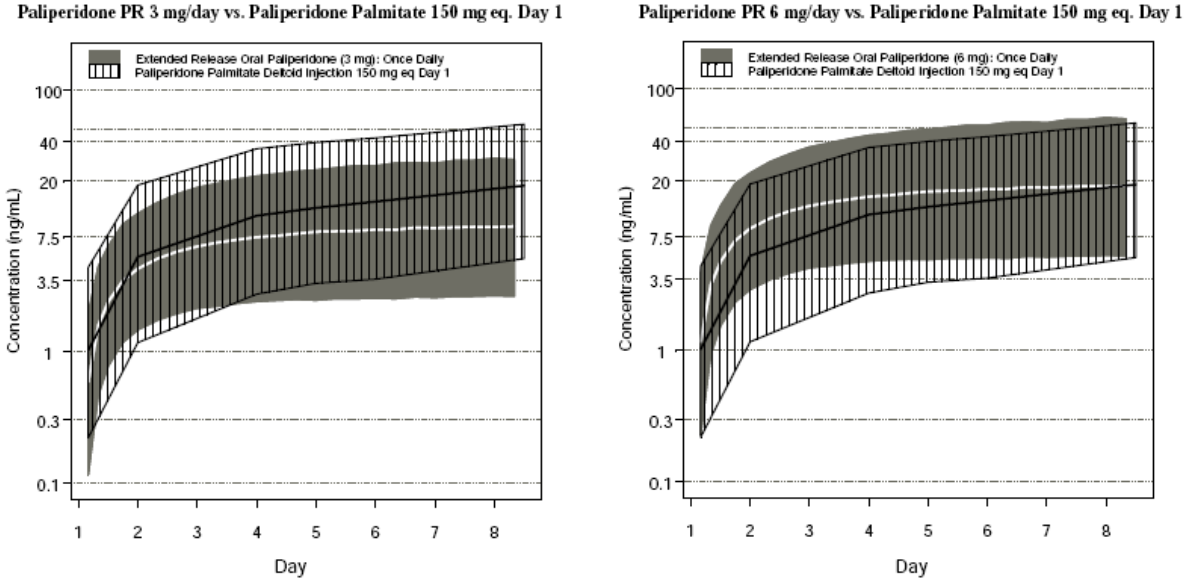
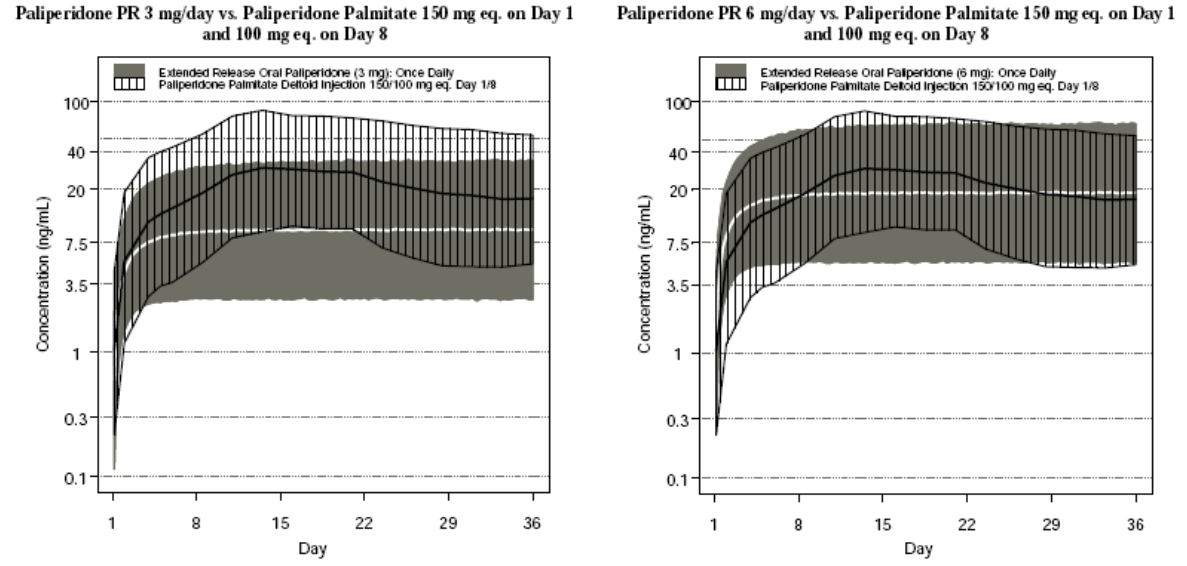
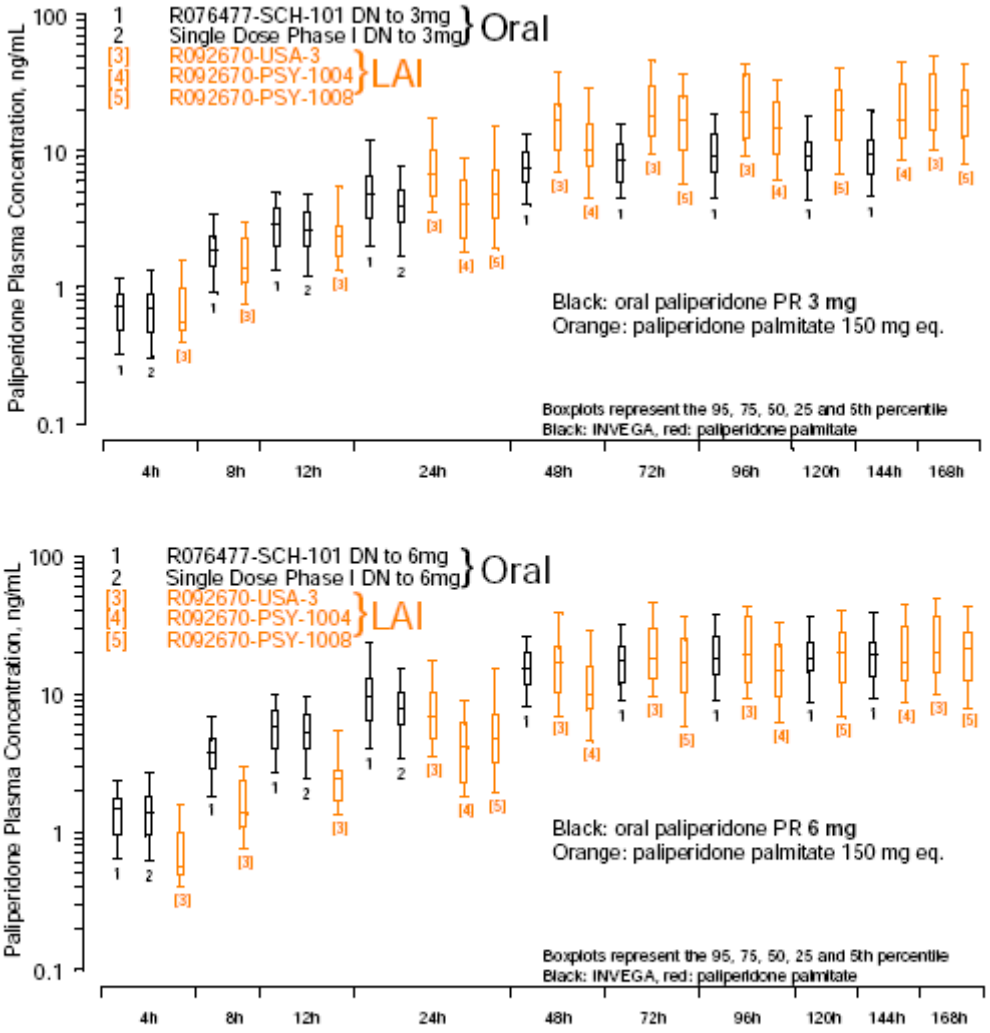


Figure 2. Simulated Paliperidone Concentration-Time Profiles for the First 5 Weeks of Treatment for Paliperidone PR vs. Paliperidone Palmitate Recommended Dosing Initiation Regimen 150 mg eq. on Day 1 and 100 mg eq. on Day 8. The white and black lines represent plasma paliperidone concentrations after administration of Paliperidone PR and Paliperidone Palmitate respectively. The shaded and hatched areas represent the 90% prediction interval based on the population PK simulation.



Observed paliperidone concentration data from several studies and plasma concentrations during the first week of treatment were also presented. In comparison with oral paliperidone 6 mg/day, the plasma concentrations of paliperidone are slightly lower only during the first 48 hours after administration of paliperidone palmitate according to the proposed dosing schedule. Paliperidone palmitate exposure was similar to 3 mg oral paliperidone (Invega) by 4 hours after injection (Figure 3).

Figure 3. Paliperidone Plasma Concentrations on Day 1 to Day 7 After Injection of Paliperidone Palmitate 150 mg eq. in the Deltoid Muscle vs. Oral Administration of Paliperidone PR 3 mg or 6 mg



Single-dose PK data up to 24 hours were used from the following studies: R076477--BIM-1003, -P01-1012, SCH-1015, SCH-1016, SCH-1017 and SCH-1018
Black boxplots (labeled with study numbers 1 and 2) represent oral paliperidone PR; orange boxplots (labeled with study numbers [3], [4], and [5]) represent paliperidone palmitate

Comparison of exposure with risperidone/paliperidone

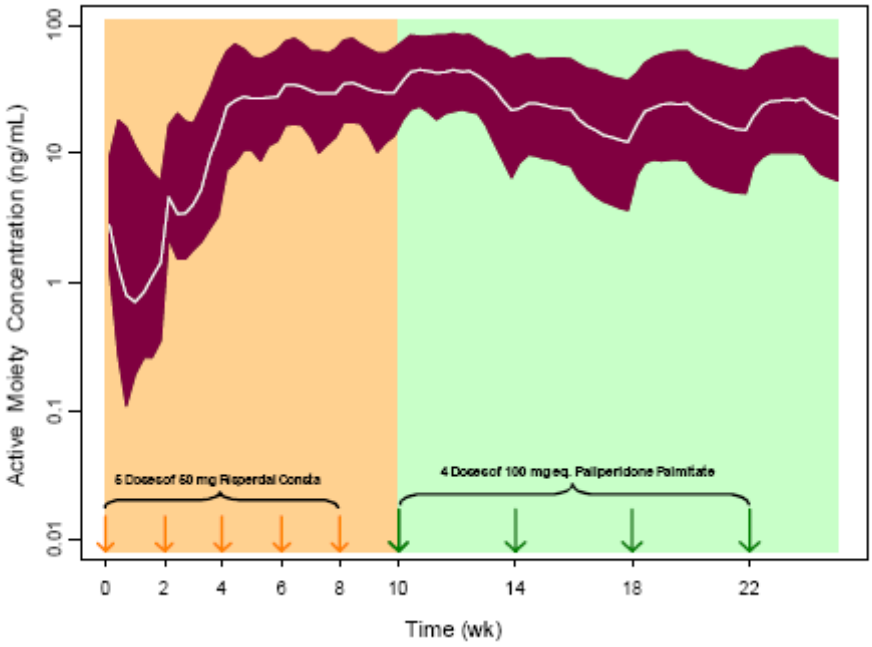
A number of simulations were provided to support the following dosing recommendation (not requiring the initial one week initiation dosing at day 1 and 8) for switching from risperidone long acting injectable to paliperidone palmitate (see Table 1):

Table1. Proposed doses of RISPERDAL CONSTA and paliperidone palmitate needed to attain similar paliperidone exposure at steady-state

Previous RISPERDAL CONSTA Dose	XEPLION Injection
25 mg every 2 weeks	50 mg monthly
37.5 mg every 2 weeks	75 mg monthly
50 mg every 2 weeks	100 mg monthly

The simulation for the highest dose (switch from 50 mg every 2 weeks of Risperdal consta to 100 mg monthly of paliperidone palmitate) is presented in Figure 4.

Figure 4: Switching From Risperdal consta to paliperidone palmitate (High Dose Scenario). Lines and shaded areas represent medians and 90% prediction intervals.



Distribution

No specific study has been performed with paliperidone palmitate and this was considered acceptable taking into account that the distribution profile of paliperidone has already been characterised with oral paliperidone studies.

Paliperidone distributed well into the brain, as evidenced by displacement of 11C-racloprine measured using PET imaging in healthy subjects. Within therapeutically relevant concentrations of 50 to 250 ng/mL, the plasma protein binding was 74% for paliperidone, 82% for (+)-paliperidone and 65% for (-)-paliperidone, and was not influenced by sex, age, or renal function. Paliperidone and its enantiomers were predominately bound to α1-acid glycoprotein and albumin. In patients with moderate hepatic impairment, plasma protein binding was reduced, mainly because of a reduction in α1-acid glycoprotein and albumin plasma concentrations.

Following im administration, the volume of distribution after administration of paliperidone palmitate was 391 L, based on population PK modelling. The observed clearance was nearly identical to the observed clearance after iv administration of paliperidone with 4.95L/h and 4.99 L/hr, respectively.

Elimination

No specific study has been performed with paliperidone palmitate and this was considered acceptable taking into account that the elimination profile of paliperidone has already been characterised with oral paliperidone studies. The plasma clearance of paliperidone (about 80 ml/min) is low relative to hepatic plasma flow (about 700 ml/min), and therefore paliperidone can be considered as a drug with a low

hepatic extraction ratio. The half-life of paliperidone is 20-25 hours and is independent of dose, route of administration and formulation. Paliperidone was mainly excreted in urine (80% of a radiolabelled dose), while only a small part was excreted in faeces (11%). Almost 60% of the dose was excreted as unchanged drug in urine. Renal clearance of unchanged paliperidone was on average 53 ml/min. About 50% of the renal clearance of unchanged paliperidone was by means of filtration (average CLGFR: 25.9 ml/min), the other half occurred by active processes (average CLact: 27.2 ml/min).

Dose proportionality and time dependencies

Dose proportionality

After a single-dose injection of paliperidone palmitate 25, 50, 100, or 150 mg eq using im route, total paliperidone exposure increased proportionally in both tested injection sites (deltoid and gluteal muscles). The increase in the observed maximum plasma concentration (Cmax) of paliperidone was less than dose proportional for doses above 50 mg eq and the t1/2 was prolonged.

Time dependency

The pharmacokinetic profile of paliperidone palmitate did not appear to be time dependent. After repeated-dose injection of paliperidone palmitate of 150 mg eq (maximum recommended dose) using im route, steady state was not reached until after 230-260 days (approximately 8 to 9 months). Actual accumulation ratios for Cmax and AUC after multiple dose were in the same range as those predicted in the single-dose administration.

Inter and Intra-individual variability

The inter-individual variability for paliperidone after administration of paliperidone palmitate is in the range 40-50%, and thus, similar to the variability for orally administered paliperidone. No data on intra-individual variability have been presented. In the population PK model, the inter-occasion variability was lower than the inter-individual variability for clearance and volume, but for bioavailability, the inter-occasion and inter-individual variability terms were equally large.

Special populations

Population pharmacokinetic analysis evaluating renal function and a number of parameters including the effect of race, gender, age was conducted. The effect of body mass index (BMI)/needle length, injection site and volume was also investigated. No studies in paediatric population with schizophrenia have been performed in accordance with the waiver granted for all subsets of this population.

In subjects with mild renal impairment (renal clearance: 50-80 mL/min) a 75 mg eq. dose resulted in a similar exposure as a 100 mg eq. dose in subjects with normal renal function (renal clearance > 80 mL/min).

Hepatic function was not evaluated in the population pharmacokinetic analysis. Available information derived from a study conducted in healthy volunteers with oral paliperidone. The exposure to paliperidone was decreased in patients with moderate hepatic impairment (Child Pugh class B) compared with healthy subjects. However, the protein levels were lower and the unbound fraction higher in the hepatically impaired group while the unbound exposure was similar in both groups. No dose adjustment is required in patients with mild or moderate hepatic impairment. Severe hepatic impairment has not been studied with oral paliperidone.

Population pharmacokinetic analysis did not reveal any clinically significant effect of race, gender nor age. When comparing the paliperidone exposure in subjects in the age range of 18-60 years with that in subjects >60 years, small differences in the pharmacokinetic profile were observed between both age groups, however the older population showed a decline in renal function.

Population pharmacokinetic analysis showed that using a 1.5-inch needle for deltoid injection in subjects with a body weight over 90 kg (corresponding to a BMI of approximately 30 kg/m2) resulted in plasma concentration-time profiles that were comparable to those obtained when using a 1-inch needle for deltoid injection in subjects with a body weight of less than 90 kg, suggesting to use a longer needle for obese patients to achieve adequate exposure to paliperidone. Compared to deltoid injections, repeated administration in the gluteal muscle resulted in a delayed time to achieve steady-state (approximately 4 weeks longer), but did not influence the overall exposure (in terms of steady-state concentrations) to paliperidone. Deltoid injections resulted in a faster rise in initial plasma concentrations. Additional data from phase III studies confirmed these findings.

Pharmacokinetic interaction studies

No pharmacokinetic interaction studies were performed with paliperidone palmitate. Available information derived from studies with oral paliperidone. However, according to CHMP scientific advice, the potential for hydrolysis-mediated reactions and the effect of various esterase inhibitors on paliperidone palmitate were investigated in vitro (see section 3.3.3).

Two in vitro studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by CYP isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. The effect of paliperidone on induction of metabolic enzymes has not been investigated. In line with observations in clinical studies where paliperidone displayed time-independent pharmacokinetics, paliperidone is not expected to cause enzyme induction or inhibition. As such, paliperidone is not expected to inhibit P-glycoprotein-(P-gp)-mediated transport of other drugs in a clinically meaningful manner. An in vitro study showed that paliperidone may be a substrate and a weak inhibitor of P-gp. No in vivo studies have been performed and the clinical relevance is unknown.

Paliperidone binds primarily to α1-acid glycoprotein and albumin. In vitro, high therapeutic concentrations of diazepam (3 µg/mL), sulfamethazine (100 µg/mL), warfarin (10 µg/mL) and carbamazepine (10 µg/mL) (all bound to albumin) caused a slight, though statistically significant increase in the free fraction of paliperidone (at 50 ng/mL), with a maximum increase of 12% (by carbamazepine, from 22.9 to 25.7%). Based upon these data, drug interaction at the level of protein binding is considered unlikely.

The main elimination route of paliperidone is renal excretion and about half of this is through active secretion in the renal tubule. Only one in vivo interaction study was performed with paliperidone, addressing the potential interaction with trimethoprim on the renal, secretory level. Trimethoprim, which was chosen due to its inhibitory effect on the organic cation transporter, had only small effects on the PK of paliperidone, e.g. an increase in Cmax and decreased AUC of total paliperidone, and unbound CL/F and AUC were not different. In the Caco-2 study described above, trimethoprim had no effect on the transport of paliperidone either. Furthermore, there was no indication that paliperidone affected the PK of trimethoprim at steady state, and a drug interaction at the level of renal secretion is considered unlikely.

Factors potentially affecting solubility, i.e. temperature and pH, were studied in vitro and no relevant increase in solubility for paliperidone palmitate was observed, suggesting that higher exposure to paliperidone and faster release were unlikely to occur . No in vivo data are available in this regards.

Multiple dosing with paroxetine caused increases in Cmax and AUC of a single dose of paliperidone by 10-15%. This increase was not considered clinically relevant.

In a published study, the effect of the P-gp inhibitor verapamil on the PK of risperidone was evaluated in Japanese subjects, and the exposure to risperidone and paliperidone increased 61% and 30%, respectively, while the half-lives were not affected. Effects of P-gp inhibitors directly on paliperidone are difficult to predict based on these data. No in vivo data are available and the clinical relevance was considered unknown.

In an interaction study with carbamazepine, plasma concentrations of paliperidone were reduced by a mean of approximately 37%. The induction effect was variable and suggested to be associated with induction of renal P-gp. Urinary excretion was slightly decreased, while renal CL of paliperidone increased about 35%.

In a study with patients stabilised on valproate (VPA) therapy, multiple dosing with oral paliperidone 12 mg/day did not affect the pharmacokinetics of VPA.

2.4.3. Pharmacodynamics

Mechanism of action

Paliperidone is a monoaminergic antagonist with a high affinity for serotoninergic (5-hydroxytryptamine [5-HT] type 2A [5HT2A]) and dopaminergic D2 receptors. Paliperidone binds also to α1-adrenergic receptors, and, with lower affinity, to H1-histaminergic and α2-adrenergic receptors. It has no affinity for cholinergic, muscarinic, or β1- and β2-adrenergic receptors.

Primary and Secondary pharmacology

Primary and secondary pharmacology have already been characterised with studies with oral paliperidone or risperidone and no specific study with paliperidone palmitate was conducted.

Notably, the correlation of plasma concentrations of paliperidone with the incidence of extrapyramidal symptoms (EPS) was analysed using a hazard model. The hazard model relates the EPS-incidence to average steady state paliperidone plasma concentrations during a 6-week oral treatment with oral paliperidone. Steady state plasma concentrations up to 20 ng/ml were not associated with an increased risk for EPS as EPS-incidences below that plasma concentration are similar to placebo (about 10%). For plasma concentrations between 20 and 40 ng/ml, the risk to develop EPS increased with a factor of 2.8 until it reaches a plateau of approximately 30%. The EC50 was estimated to be 24 ng/ml. It has been suggested that D2-receptor occupancies above 80% are associated with an increased risk for EPS. An average steady state plasma concentration of paliperidone of 24 ng/ml corresponds to a D2-receptor occupancy of approximately 83% (KDapp: mean ± SD: 4.9 ± 0.53 ng/ml). This is consistent with other reports in the literature that suggest that increased risk to develop EPS is associated with D2-receptor occupancies of > 80%.

Based on the in vitro and in vivo PK properties of paliperidone, the probability of drug-drug interactions is low. However, considering the drug's primary effects on the CNS, paliperidone should be administered with caution in combination with other centrally active drugs. Paliperidone may

antagonize the effects of levodopa and other dopamine agonists. Due to its alpha>-adrenergic receptor antagonism, paliperidone has the potential to enhance the effect of certain antihypertensive agents.

No data are available on genetic differences in pharmacodynamic response. A review of publications on paliperidone (as metabolite of risperidone) indicated that exposure to paliperidone in diverse groups of subjects that included subjects with genetic polymorphisms was generally tolerated.

2.4.4. Discussion on clinical pharmacology

The absorption and distribution profile of paliperidone palmitate has been adequately characterised. Available information on the metabolism and elimination derived from studies with oral paliperidone and this is considered acceptable taking into consideration that the systemic exposure to paliperidone palmitate is low, due to extensive hydrolysis into paliperidone and palmitic acid. In several studies, concentrations of paliperidone palmitate in plasma was detectable in a limited number of samples (2.5% of the samples analyzed).

Following a single im dose of paliperidone palmitate, plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median tmax of 14 days (12-16 days). The release of the drug starts as early as Day 1 and the apparent half-life for paliperidone ranged from 25-49 days, depending on the doses. The absolute bioavailability of paliperidone using i.m. administration of paliperidone palmitate was estimated to be complete based on the comparison between i.m. routes of paliperidone palmitate and immediate release (IR) paliperidone. Following im administration, the volume of distribution after administration of paliperidone palmitate was 391 L, based on population PK modelling. The observed clearance was nearly identical to the observed clearance after iv administration of paliperidone with 4.95L/h and 4.99 L/hr, respectively, supporting the complete bioavailability of paliperidone after paliperidone palmitate injection.

However, effects of injection site/volume, BMI on absorption were observed. On this basis, specific recommendations for the site of administration (injection at the deltoid muscle) and the use of the needle length (longer needle required for patient≥ 90 kg) were proposed by the applicant. These were questioned by the CHMP in light of the data from phase III studies (see section 3.5).

Furthermore, no direct comparison with exposure to oral paliperidone was performed and this was raised by the CHMP in light of the broad indication applied for *"treatment of schizophrenia in adults".* Pharmacokinetic data on oral paliperidone and paliperidone palmitate collected from study SCH-201, suggested comparable exposure for Invega 6 mg/day and paliperidone palmitate 75 mg eq./month. However; the study design was not reflecting the proposed dosing schedule for XEPLION: a dose of 150 mg on initial treatment day 1 and a dose of 100 mg on day 8 thereafter a monthly recommended maintenance dose of 75 mg. Furthermore, the design included an oral run-in period with paliperidone for 7 days without a washout-phase, therefore allowing an overlap of plasma levels from oral and i.m-treatment and the formulation intended to be marketed (F013) was not used in this study. Nonetheless, the CHMP considered the PK simulations provided by the applicant and concluded that these were valid. Both simulated and observed plasma concentration data showed that for paliperidone palmitate, plasma concentrations of paliperidone that appeared lower only during the first days of treatment in comparison with oral administration of Invega 6 mg/day were achieved with the proposed dosing regimen.

Regarding switching from risperidone long acting injectable (Risperdal consta) to paliperidone palmitate, the CHMP considered that adequate simulation were provided to support the proposed dosing recommendation (not requiring the one week initiation regimen at day 1 and 8). This is further

supported by the maintenance of the steady-state concentrations after the last injection of Risperdal consta for 4–5 weeks and decline thereafter with a mean plasma half-life of 4–6 days.

In accordance with the CHMP scientific advice, no specific phase I studies were conducted in the elderly population and information related to hepatic impairment reflected in the SPC derived from oral paliperidone. No dose adjustment is required in patients with mild or moderate hepatic impairment and caution is recommended in patients with severe hepatic impairment in the absence of data.

Population pharmacokinetic analysis with paliperidone palmitate did not indicate differences regarding renal function and effects of race, nor age between paliperidone palmitate and oral paliperidone. No clinically significant differences were observed between men and women. Similarly to oral paliperidone, no dose adjustment is recommended in patients with mild renal impairment. However paliperidone palmitate is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min).

In accordance with the CHMP scientific advice, no specific interaction studies were performed with paliperidone palmitate apart from those related to esterase-mediated hydrolysis (see section 3.3.3).

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacological profile of paliperidone palmitate in human studies has been adequately characterised.

2.5. Clinical efficacy

The initial indication applied for is: treatment of adult patients with schizophrenia.

The clinical development included short term and long term studies. Short-term efficacy was studied in four placebo controlled, dose-finding, fixed dose studies as well as in two flexible dose, non-inferiority studies (versus Risperdal Consta, without a placebo group). Maintenance of effect was studied in one placebo controlled, flexibly dosed, relapse prevention study and one flexible dose, non-inferiority study (versus Risperdal Consta without a placebo control). The injection site and the needle size have varied between the studies.

A tabulated summary of the studies are presented in Table 2.

Table 2. Efficacy studies

Study	Objective	Design	Dosing	Injection site	Duration
SCH-201	Short-term efficacy, dose-response	DB, placebo, 2 fixed doses	50 or 100 mg at day 1, 8 and 36	Gluteal muscle	9 weeks
PSY-3003	Short-term efficacy, dose-response	DB, placebo, 3 fixed doses	50, 100 or 150 mg at day 1, 8, 36 and 64	Gluteal muscle	13 weeks
PSY-3004	Short-term efficacy, dose-response	DB, placebo, 3 fixed doses	25, 50 or 100 mg at day 1, 8, 36 and 64	Gluteal muscle	13 weeks
PSY-3007	Short-term efficacy, dose-response	DB, placebo, 3 fixed doses	150 mg day 1 followed by 25, 100 or 150 mg day 8, 36 and 64	First injection in deltoid muscle, following injections in deltoid or gluteal muscle	13 weeks
PSY-3006	Short-term efficacy, non-inferiority vs Risperdal Consta every 2 weeks	DB, double dummy, flexible doses	150 mg day 1, 100 mg day 8, 50 or 100 mg day 36, 50, 100 or 150 mg day 64	First two injections in deltoid muscle, following injections in deltoid or gluteal muscle	13 weeks
PSY-3008	Short-term efficacy, non-inferiority vs Risperdal Consta every 2 weeks	Open label, rater blinded, flexible doses Risperdal consta flexible dose 25-50 mg plus oral supplementation risperidone	150 mg day 1, 100 mg day 8, 50 or 100 mg day 36, 50, 100 or 150 mg day 64	First two injections in deltoid muscle, following injections in deltoid or gluteal muscle	13 weeks
PSY-3001	Maintenance of effect, relapse prevention	DB, placebo, flexible dose	25-100 mg during maintenance and DB phase	Gluteal muscle	33 weeks open label, variable DB phase, 52 weeks open label extension
PSY-3002	Maintenance of effect, non-inferiorirty vs Risperdal Consta every 2 weeks	DB, flexible dose Risperdal consta flexible dose 25, 37.5 or 50 mg	25-100 mg every 4 weeks	Gluteal muscle	53 weeks

DB: double blind

2.5.1. Dose response study

Dose-response was evaluated in the short term studies (phase II/III: SCH-201, phase III: PSY-3003, -3004, -3007). The results of the dose-response are presented in section 3.5.2.

2.5.2. Main studies

2.5.2.1. Short term studies

2.5.2.1.1. Methods

The short-term studies were designed as follows:

- SCH- 201: a phase II/III 9 week randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of 50 and 100 mg eq. of paliperidone palmitate in subjects with schizophrenia, conducted in Poland, Bulgaria, Russia, Ukraine, the United States,India.

- PSY-3003: a phase III 13 week randomised, double-blind, placebo-controlled, parallel group fixed dose study to evaluate the efficacy and safety of 50, 100 and 150 mg eq. of paliperidone palmitate in subjects with schizophrenia, conducted in Ukraine, Korea, Malaysia, Taiwan and the United States.

- PSY-3004: a phase III 13 week randomised, double-blind, placebo-controlled, parallel group fixed dose study to evaluate the efficacy and safety of 25, 50 and 100 mg eq. of paliperidone palmitate in subjects with schizophrenia, conducted Bulgaria, Romania, Russia, South Africa and the United States.

- PSY-3007: a phase III 13 week randomised, double-blind, placebo-controlled, parallel group , fixed dose, study to evaluate the efficacy and safety of 25, 50 and 100 mg eq. of paliperidone palmitate in subjects with schizophrenia, conducted in Romania, Serbia, Montenegr Ukraine, Russia,Korea, Malaysia, Taiwan and the United States.

- PSY-3006: a phase III 13 week randomised, double-blind, active-controlled, parallel group study to evaluate the efficacy and safety of paliperidone palmitate versus risperidone long acting intramuscular injection in subjects with schizophrenia ,conducted in Austria, Czech Republic, Estonia, France, Germany, Hungary, Lithuania, Poland, Spain Bulgaria, Ukraine, Russia, India and the United States

- PSY 3008: a phase III 13 week open label, parallel group, fixed dose study to evaluate efficacy of Paliperidone Palmitate (50, 100, or 150 mg eq.) and Risperidone Long Acting Injection (25, 37.5, or 50 mg) in subjects with schizophrenia (The approximate length of the study for each subject was 14 weeks, including a screening period of no more than 7 days and a 13-week open-label treatment period. This study was conducted in China.

Study participants

Main inclusion criteria

Male or female, 18 years of age or older, fulfilling the DSM-IV criteria for schizophrenia since at least one year, and have a screening/baseline PANSS score of at least 60 or 70 and a maximum score of 120.

Main exclusion criteria

Exclusion criteria mainly included: any primary active DSM-IV diagnosis other than schizophrenia, patients treated with long acting injectable (LAI) antipsychotics, Electroconvulsive therapy (ECT), monoamine oxydase (MAO)-inhibitors, any other anti depressants (unless on a stable dose for at least 30 days), oral antipsychotics or mood stabilizers within different specified time limits; a decrease of at

least 25% in PANSS total score between screening and baseline; a significant risk of suicidal or violent behavior.

Treatments

In all short term studies, paliperidone palmitate was administered at day 1 and 8 and every 4 weeks thereafter and included a screening period up to 5 days for wash-out of psychotropic medications other than allowed antidepressants. Prior to entering the double blind treatment phase, there was a 7 day oral run in period in study SCH-201(6 mg or 12 mg extended release paliperidone or 2 mg or 4 mg immediate release paliperidone) and a 4 day tolerability testing was performed for subjects not previously exposed to risperidone or paliperidone in the other short term studies.

In studies SCH-201, PSY-3003, PSY-3004, the allocated dose was administered at all time points and exclusively in a gluteal muscle. In study PSY-3007, all actively dosed patients started with 150 mg administered in a deltoid muscle followed by deltoid or gluteal muscle injections (at the discretion of the investigator) of different doses. In studies PSY-3006 and -3008, the first two doses, 150 and 100 mg, respectively, were administered in a deltoid muscle followed by flexible doses (50-150 mg) administered as deltoid or gluteal injections. In studies PSY-3007, -3006 and -3008, the needle length was additionally weight adjusted for the deltoid muscle injections.

Outcomes/endpoints

The primary endpoint was change from baseline in total score on the Positive And Negative Syndrome Scale (PANSS). Main secondary endpoints included the Personal and Social Performance (PSP) scale, and Clinical Global Impression of Severity (CGI-S) and the responder rate (defined as a 30% or more reduction from Day 1 in the total PANSS score to endpoint).

Sample size

In placebo controlled studies, the sample size calculation was 90% power to detect a difference of at least 10 points (except study PSY-3007 which used a difference of at least 9 points) in change from baseline in total PANSS at a two-sided significance level of 0.10. In non-inferiority studies, the margin was set to a difference of 5 to 5.5 points. The power was specified to 80 % at a one-sided significance level of 0.025.

Randomisation

In study SCH-201, at day -7 predose, eligible subjects were sequentially assigned within each site to one of the 4 oral run opel label groups. Sequential medication code numbers were printed on the single-panel study drugs labels, and subject numbers were inserted at the time of dispensing.

In all short term studies, eligible subjects were randomly assigned at baseline in a specified ratio and according to a computer-generated randomisation schedule prepared by the sponsor prior to the study. Randomisation was balanced by using permuted blocks and was stratified by center. Central randomisation was used via interactive voice response system (IVRS).

Blinding (masking)

Placebo and active drug differed in appearance. To keep the blinding, double dummy technique was used (when applicable) and treatment was administered by a dedicated staff who was not allowed to take part in any other study activities or study related discussions with other study personnel. Prolactin levels were not available to investigator or the sponsor during the study period. In study PSY-3008 (open label), efficacy assessment was performed with independent evaluator at each site who were blinded to treatment assignment.

Statistical methods

In placebo controlled studies, efficacy was evaluated in the Intention-To-Treat (ITT) population defined as all randomised patients who had received at least one dose of study medication, and who had both a baseline and at least one post baseline efficacy evaluation. In study PSY-3003, it was also required that the allocated dose was not changed during the study, in contrast to the other studies in which a change of dose was not disqualifying for inclusion in the ITT population. In non-inferiority studies, efficacy was evaluated in the ITT population as well as in a Per Protocol (PP) population. For inclusion in the PP population at least 36 days of double blind treatment (i.e. at least 3 injections) was required.

In all short term studies, the PANSS score was analysed using an ANCOVA model with study centre or country and baseline value as covariates. The CGI score used an ANCOVA analysis based on ranks. Categorical variables were analysed with the Cochran-Mantel-Haenszel test controlling for study centre or country. In non-inferiority studies, the 95 % confidence intervals were based on the ANCOVA analyses. Dunnett's test or a Dunnett-Bonferroni procedure was used to adjust for multiple comparisons of different doses against placebo. The Last Observation Carried Forward (LOCF) approach was used for missing values for the efficacy variables.

2.5.2.1.2. Results

Results from placebo controlled studies (SCH-201, PSY-3003,-3004 and -3007) and non inferiority studies (PSY-3006, -3008) are presented separately.

2.5.2.1.2.1. Placebo controlled short term studies

Participant flow

This is presented in Tables 3, 4 and 5.

Table 3 Completion and withdrawal in Study SCH-201. All randomised subjects.

		R092670		
	Placebo (N=84) n (%)	50 mg eq. (N=79) n (%)	100 mg eq. (N=84) n (%)	Total (N=247) n (%)
Completed	27 (32)	47 (59)	51 (61)	125 (51)
Withdrawn	57 (68)	32 (41)	33 (39)	122 (49)
Subject choice (subject withdrew consent)	8 (10)	4 (5)	11 (13)	23 (9)
Lost to follow-up	2 (2)	1 (1)	4 (5)	7 (3)
Adverse event	8 (10)	3 (4)	2 (2)	13 (5)
Lack of efficacy	36 (43)	23 (29)	14 (17)	73 (30)
Other[a]	3 (4)	1 (1)	2 (2)	6 (2)

[a] Includes noncompliance (n=4), sponsor decision (n=1), and unavailability of study drug injection.

Table 4 Completion and withdrawal in Study PSY-3003 and PSY-3004. All randomised subjects

		R092670					
	Placebo	25 mg eq.	50 mg eq.	100 mg eq.	150 mg eq.	150 mg eq./Pbo [a]	Total Pali. Palmitate
	n (%)	n (%)	N (%)	n (%)	n (%)	n (%)	n (%)
R092670-PSY-3003	(N=136)	-	(N=94)	(N=97)	(N=30)	(N=31)	(N=221)
Completed	51 (38)	-	47 (50)	53 (55)	12 (40)	24 (77)	112 (51)
Withdrawn	85 (63)	-	47 (50)	44 (45)	18 (60)	7 (23)	109 (49)
Lack of efficacy	48 (35)	-	25 (27)	26 (27)	13 (43)	3 (10)	64 (29)
Subject choice[b]	12 (9)	-	7 (7)	9 (9)	2 (7)	2 (6)	18 (8)
Adverse event	13 (10)	-	8 (9)	2 (2)	2 (7)	0	12 (5)
Lost to follow-up	4 (3)	-	4 (4)	4 (4)	1 (3)	1 (3)	9 (4)
Other	8 (6)	-	3 (3)	3 (3)	0	1 (3)	6 (3)
R092670-PSY-3004	(N=127)	(N=131)	(N=129)	(N=131)	-	-	(N=391)
Completed	48 (38)	70 (53)	70 (54)	75 (57)	-	-	215 (55)
Withdrawn	79 (62)	61 (47)	59 (46)	56 (43)	-	-	176 (45)
Lack of efficacy	45 (35)	31 (24)	31 (24)	21 (16)	-	-	83 (21)
Subject choice[b]	12 (9)	9 (7)	14 (11)	11 (8)	-	-	34 (9)
Adverse event	8 (6)	8 (6)	2 (2)	6 (5)	-	-	16 (4)
Lost to follow-up	10 (8)	8 (6)	4 (3)	13 (10)	-	-	25 (6)
Death	1 (1)	0	0	1 (1)	-	-	1 (<1)
Other	3 (2)	5 (4)	8 (6)	4 (3)	-	-	17 (4)
Pooled Studies	(N=263)	(N=131)	(N=223)	(N=228)	(N=30)	(N=31)	(N=612)
Completed	99 (38)	70 (53)	117 (52)	128 (56)	12 (40)	24 (77)	327 (53)
Withdrawn	164 (62)	61 (47)	106 (48)	100 (44)	18 (60)	7 (23)	285 (47)
Lack of efficacy	93 (35)	31 (24)	56 (25)	47 (21)	13 (43)	3 (10)	147 (24)
Subject choice[b]	24 (9)	9 (7)	21 (9)	20 (9)	2 (7)	2 (6)	52 (8)
Adverse event	21 (8)	8 (6)	10 (4)	8 (4)	2 (7)	0	28 (5)
Lost to follow-up	14 (5)	8 (6)	8 (4)	17 (7)	1 (3)	1 (3)	34 (6)
Death	1 (<1)	0	0	1 (<1)	0	0	1 (<1)
Other	11 (4)	5 (4)	11 (5)	7 (3)	0	1 (3)	23 (4)

[a] This group is not included in the total column
[b] Subject withdrew consent

Table 5 Completion and withdrawal in Study PSY-3007. All randomised subjects.

	Placebo (N=164) n (%)	**R092670** 25 mg eq. (N=160) n (%)	**R092670** 100 mg eq. (N=165) n (%)	**R092670** 150 mg eq. (N=163) n (%)	Total (N=652) n (%)
Completed	71 (43)	83 (52)	89 (54)	90 (55)	333 (51)
Withdrawn	93 (57)	77 (48)	76 (46)	73 (45)	319 (49)
Lack of efficacy	45 (27)	31 (19)	28 (17)	23 (14)	127 (19)
Subject choice (subject withdrew consent)	26 (16)	23 (14)	28 (17)	30 (18)	107 (16)
Adverse event	11 (7)	10 (6)	10 (6)	13 (8)	44 (7)
Lost to follow-up	9 (5)	12 (8)	6 (4)	6 (4)	33 (5)
Pregnancy	0	0	1 (1)	0	1 (<1)
Other	2 (1)	1 (1)	3 (2)	1 (1)	7 (1)

Baseline data

These are presented in Tables 6, 7 and 8.

Table 6 Diagnosis and psychiatric history at baseline in Study SCH-201. ITT set.

		R092670		
	Placebo (N=66)	50 mg eq. (N=63)	100 mg eq. (N=68)	Total (N=197)
Schizophrenia type, n (%)				
N	66	63	68	197
Paranoid (295.30)	58 (88)	56 (89)	60 (88)	174 (88)
Disorganized (295.10)	1 (2)	1 (2)	0	2 (1)
Undifferentiated (295.90)	4 (6)	4 (6)	6 (9)	14 (7)
Residual (295.60)	3 (5)	2 (3)	2 (3)	7 (4)
Age at diagnosis of schizophrenia (yrs)				
N	65	62	68	195
Mean (SD)	28.0 (9.42)	27.0 (8.66)	24.8 (7.17)	26.6 (8.51)
Median	26.0	26.5	23.0	25.0
Range	(15;55)	(6;46)	(12;46)	(6;55)
Baseline PANSS total score				
N	66	63	68	197
Mean (SD)	87.8 (13.90)	88.0 (12.39)	85.2 (11.09)	87.0 (12.50)
Median	86.0	87.0	85.0	86.0
Range	(55;118)	(64;120)	(66;118)	(55;120)
Baseline CGI-S, n (%)				
N	66	63	68	197
Mild	6 (9)	3 (5)	6 (9)	15 (8)
Moderate	26 (39)	27 (43)	32 (47)	85 (43)
Marked	28 (42)	27 (43)	26 (38)	81 (41)
Severe	6 (9)	6 (10)	4 (6)	16 (8)
Antipsychotic use, n (%)				
N	66	63	68	197
Yes	49 (74)	47 (75)	51 (75)	147 (75)
No	17 (26)	16 (25)	17 (25)	50 (25)
Time since last psychotic episode (days)				
N	51	52	51	154
Mean (SD)	416.4 (744.66)	345.2 (458.29)	296.9 (372.77)	352.8 (546.85)
Median	94.0	211.5	141.0	145.5
Range	(4;3564)	(2;1782)	(3;1268)	(2;3564)
Prior hospitalizations for psychosis, n (%)				
N	61	62	67	190
1	11 (18)	11 (18)	6 (9)	28 (15)
2	10 (16)	9 (15)	16 (24)	35 (18)
3	10 (16)	11 (18)	15 (22)	36 (19)
≥4	30 (49)	31 (50)	30 (45)	91 (48)

Table 7 Diagnosis and psychiatric history at baseline in Study PSY-3003 and PSY-3004. ITT set.

	Placebo (N=257)	R092670 25 mg eq. (N=130)	R092670 50 mg eq. (N=221)	R092670 100 mg eq. (N=225)	R092670 150 mg eq. (N=30)	Total Pali. Palmitate (N=606)
Schizophrenia type, n (%)						
N	257	130	221	225	30	606
Paranoid (295.30)	224 (87)	120 (92)	184 (83)	195 (87)	25 (83)	524 (86)
Disorganized (295.10)	3 (1)	1 (1)	5 (2)	7 (3)	0	13 (2)
Catatonic (295.20)	3 (1)	0	2 (1)	0	0	2 (<1)
Undifferentiated (295.90)	24 (9)	9 (7)	29 (13)	23 (10)	5 (17)	66 (11)
Residual (295.60)	3 (1)	0	1 (<1)	0	0	1 (<1)
Age at diagnosis of schizophrenia (yrs)						
N	256	128	221	225	30	604
Mean (SD)	26.4 (9.12)	26.5 (9.12)	24.5 (8.38)	26.4 (9.03)	23.7 (5.81)	25.6 (8.72)
Median	25.0	25.0	23.0	24.0	22.5	23.0
Range	(7;56)	(13;51)	(6;52)	(10;55)	(16;40)	(6;55)
Baseline PANSS total score						
N	257	130	221	225	30	606
Mean (SD)	91.5 (12.39)	90.6 (12.22)	90.6 (11.50)	90.5 (11.66)	92.2 (11.72)	90.7 (11.70)
Median	89.0	88.0	89.0	89.0	92.5	89.0
Range	(70;120)	(70;120)	(70;120)	(70;119)	(72;120)	(70;120)
Baseline CGI-S, n (%)						
N	257	130	221	225	30	606
Very mild	2 (1)	0	1 (<1)	1 (<1)	0	2 (<1)
Mild	6 (2)	2 (2)	8 (4)	11 (5)	1 (3)	22 (4)
Moderate	126 (49)	59 (45)	97 (44)	105 (47)	13 (43)	274 (45)
Marked	101 (39)	61 (47)	101 (46)	89 (40)	14 (47)	265 (44)
Severe	21 (8)	8 (6)	14 (6)	19 (8)	2 (7)	43 (7)
Extremely severe	1 (<1)	0	0	0	0	0
Prior hospitalization[a], n (%)						
N	257	130	220	225	29	604
None	21 (8)	3 (2)	11 (5)	13 (6)	2 (7)	29 (5)
Once	40 (16)	22 (17)	54 (25)	36 (16)	7 (24)	119 (20)
Twice	47 (18)	20 (15)	39 (18)	37 (16)	4 (14)	100 (17)
Three times	43 (17)	20 (15)	34 (15)	48 (21)	4 (14)	106 (18)
Four times or more	106 (41)	65 (50)	82 (37)	91 (40)	12 (41)	250 (41)

[a] Prior hospitalization for psychosis, excluding the current hospitalization.

Table 8 Diagnosis and psychiatric history at baseline in Study PSY-3007. ITT set.

	Placebo (N=160)	R092670 25 mg eq. (N=155)	R092670 100 mg eq. (N=161)	R092670 150 mg eq. (N=160)	Total (N=636)
Schizophrenia type, n (%)					
N	160	155	161	160	636
Paranoid (295.30)	135 (84)	137 (88)	146 (91)	140 (88)	558 (88)
Disorganized (295.10)	7 (4)	5 (3)	3 (2)	2 (1)	17 (3)
Catatonic (295.20)	1 (1)	1 (1)	0	0	2 (<1)
Undifferentiated (295.90)	16 (10)	10 (6)	10 (6)	18 (11)	54 (8)
Residual (295.60)	1 (1)	2 (1)	2 (1)	0	5 (1)
Age at diagnosis of schizophrenia (yrs)					
N	160	155	161	160	636
Mean (SD)	26.0 (8.12)	24.4 (7.04)	26.0 (9.37)	25.0 (7.86)	25.4 (8.16)
Median	23.5	23.0	24.0	23.0	23.0
Range	(13;51)	(13;48)	(6;68)	(8;50)	(6;68)
Baseline total PANSS					
N	160	155	161	160	636
Mean (SD)	86.8 (10.31)	86.9 (11.99)	86.2 (10.77)	88.4 (11.70)	87.1 (11.21)
Median	86.0	86.0	86.0	88.0	86.0
Range	(65;113)	(61;119)	(61;112)	(64;131)	(61;131)
Baseline CGI-S, n (%)					
N	160	154	161	160	635
Mild	2 (1)	3 (2)	8 (5)	3 (2)	16 (3)
Moderate	75 (47)	79 (51)	81 (50)	72 (45)	307 (48)
Marked	73 (46)	60 (39)	68 (42)	74 (46)	275 (43)
Severe	10 (6)	12 (8)	4 (2)	11 (7)	37 (6)
Prior hospitalization[a], n (%)					
N	160	155	161	160	636
None	8 (5)	11 (7)	8 (5)	14 (9)	41 (6)
Once	30 (19)	26 (17)	32 (20)	26 (16)	114 (18)
Twice	30 (19)	25 (16)	31 (19)	28 (18)	114 (18)
Three times	20 (13)	21 (14)	29 (18)	18 (11)	88 (14)
Four times or more	72 (45)	72 (46)	61 (38)	74 (46)	279 (44)

[a]: Prior hospitalization for psychosis, excluding the current hospitalization.

Outcomes and estimation

Study SCH-201

Table 9 Primary and key secondary results in Study SCH-201. ITT set (excluding six sites), LOCF

Endpoint	**Placebo N=66**	**R092670 50 mg N=63**	**R092670 100 mg N=68**
PANSS, Change from baseline P-value vs placebo*	6.2	-5.2 0.001	-7.8 <0.0001
Responders (%), ≥30% improvement P-value vs placebo*	13.6	33.3 0.007	36.8 0.002
CGI-S, % with at least marked severity P-value vs placebo*#	50	37 0.004	32 <0.001

*) Unadjusted for multiplicity, #) ANCOVA analysis based on ranks

Due to an incorrect use of the IVRS, patients at six study sites were not given the appropriate paliperidone palmitate dose. Prior to data base lock and unblinding it was decided to exclude these sites from the primary analysis. The results for the primary and key secondary endpoints are given in Table E8. In sensitivity analysis including the six study sites excluded from the primary analysis

consistent result were shown. Similarly, consistent results were demonstrated in the worst case analysis.

Study PSY-3003

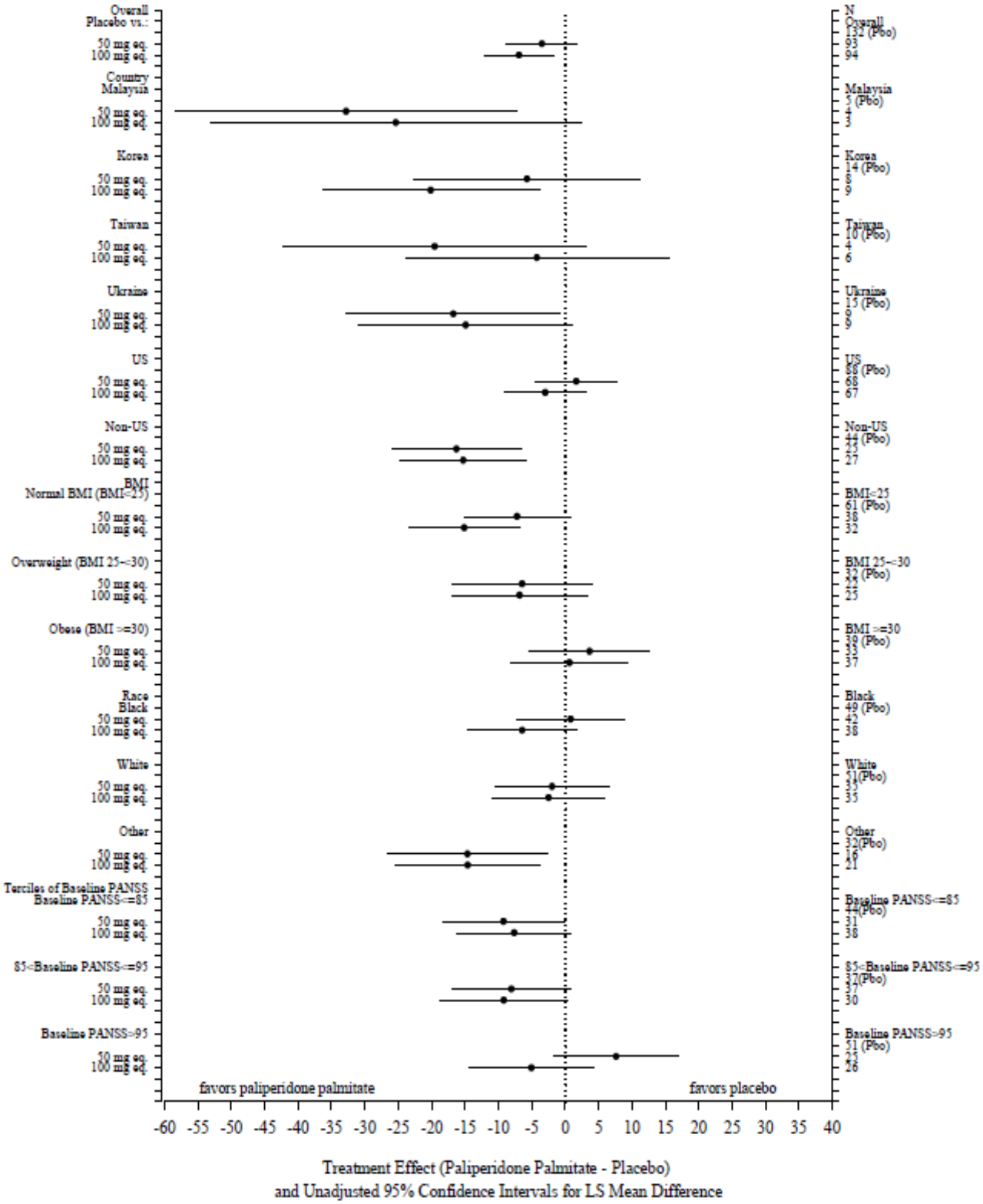
Table 10 Primary and key secondary results in Study PSY-3003. ITT set, LOCF

Endpoint	**Placebo N=132**	**R092670 50 mg N=93**	**R092670 100 mg N=94**	**R092670 150 mg N=30**
PANSS, Change from baseline P-value vs placebo*	-4.1	-7.9 0.193	-11.0 0.019	-5-5 NS
Responders (%), ≥30% improvement P-value vs placebo§	23.5	34.4 0.076	39.4 0.012	23.3 NS
PSP, Change from baseline P-value vs placebo§	-1.2	4.2 0.004	4.8 <0.001	0.6 NS
CGI-S, % with at least marked severity P-value vs placebo§#	46.7	35.5 0.069	37.2 0.010	40.0 NS

*) Adjusted for multiplicity, §) Unadjusted for multiplicity, #) ANCOVA analysis based on ranks, NS: non significant

Statistically significant ($p<0.10$) treatment-by-country and treatment-by- baseline PANSS score interactions were seen in the primary efficacy model (Figure 5).

Figure 5 Forest plot for sub-groups based on baseline characteristics in Study PSY-3003



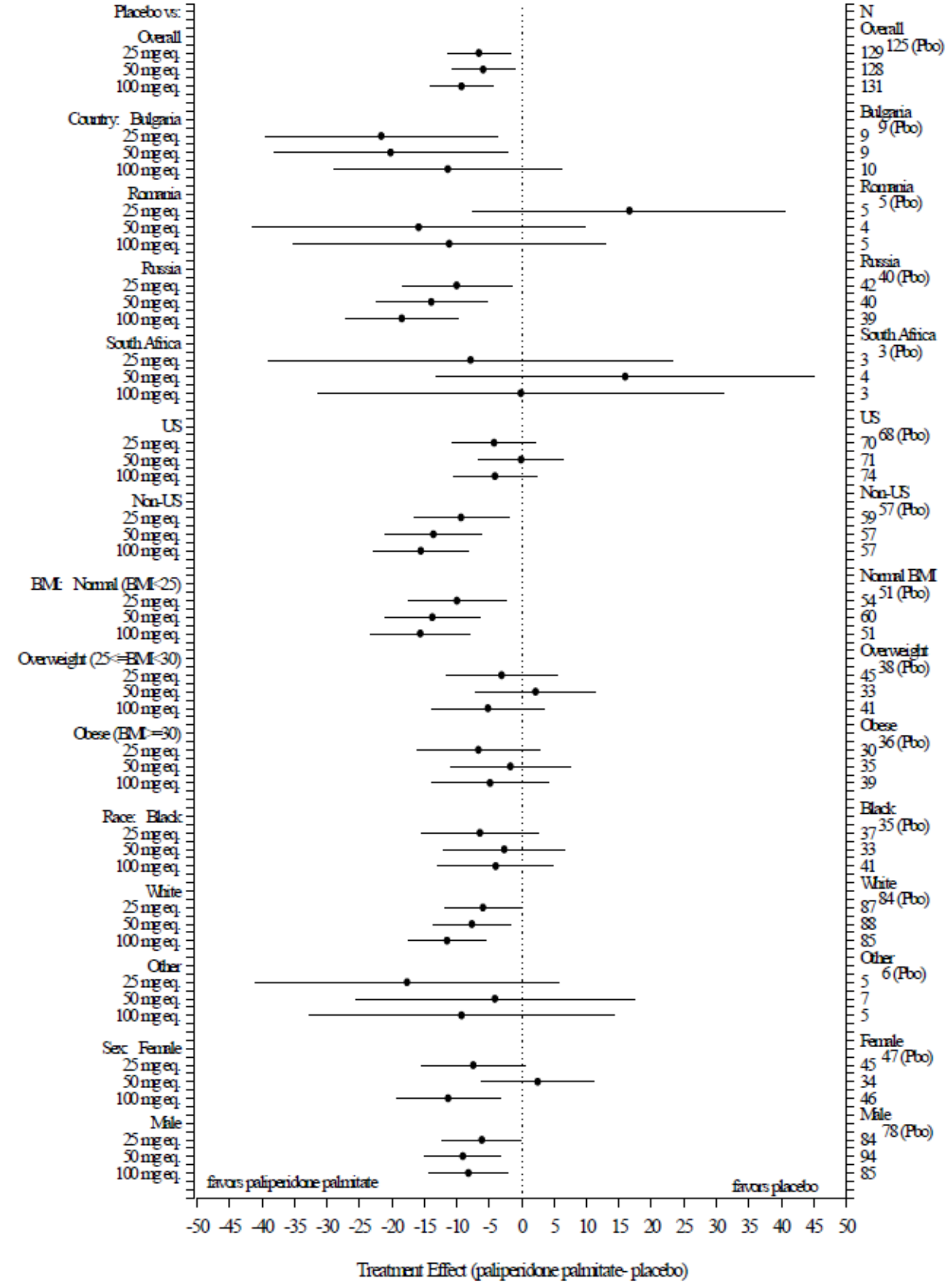
Study PSY-3004

Table 11 Primary and key secondary results in Study PSY-3004. ITT set, LOCF

Endpoint	**Placebo N=125**	**R092670 25 mg N=130**	**R092670 50 mg N=128**	**R092670 100 mg N=131**
PANSS, Change from baseline P-value vs placebo*	-7.0	-13.6 0.015	-13.2 0.017	-16.1 <0.001
Responders (%), ≥30% improvement P-value vs placebo§	31.2	45.7 0.015	37.5 0.271	51.9 <0.001
PSP, Change from baseline P-value vs placebo*	3.6	6.5 0.154	6.8 0.189	7.4 0.110
CGI-S, % with at least marked severity P-value vs placebo§#	38.4	30.2 0.003	25.8 0.006	26.0 0.002

*) Adjusted for multiplicity, §) Unadjusted for multiplicity, #) ANCOVA analysis based on ranks

Figure 6 Forest plot for sub-groups based on baseline characteristics in Study PSY-3004



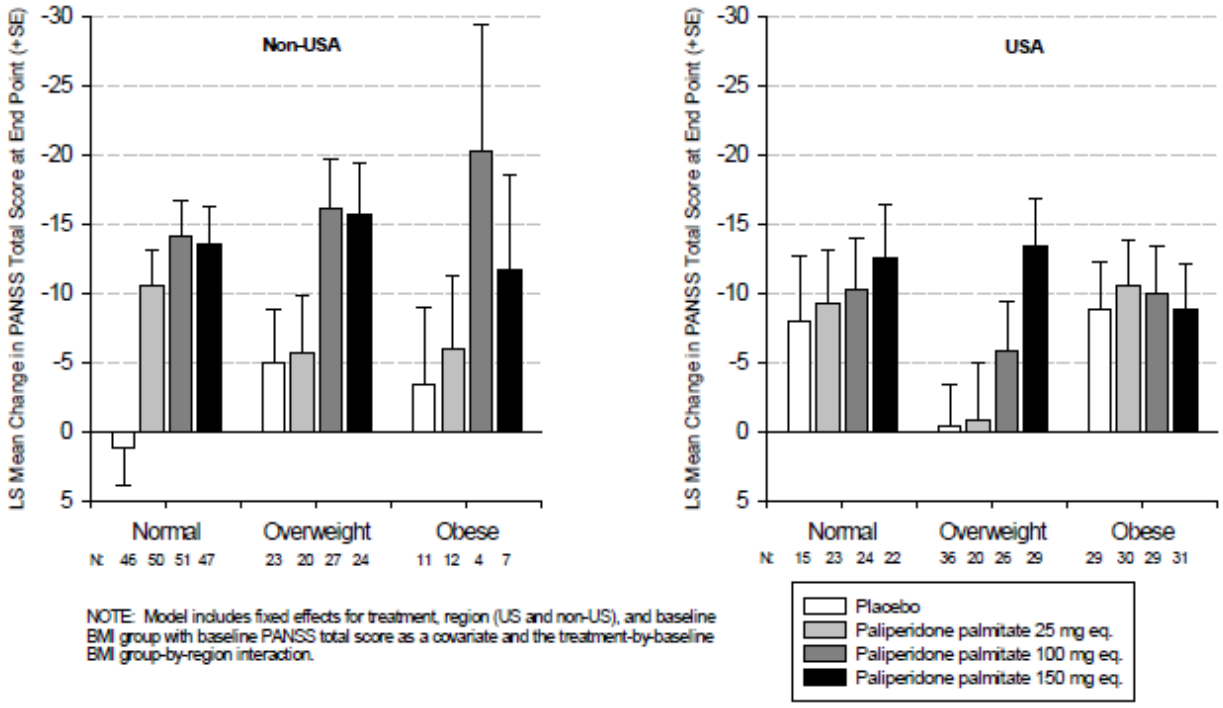
Study PSY-3007

Table 12 Primary and key secondary results in Study PSY-3007. ITT set, LOCF

Endpoint	Placebo N=160	R092670 25 mg N=155	R092670 100 mg N=161	R092670 150 mg N=160
PANSS, Change from baseline P-value vs placebo*	-2.9	-8.0 0.034	-11.6 <0.001	-13.2 <0.001
Responders (%), ≥30% improvement P-value vs placebo§	20.0	33.5 0.007	41.0 <0.001	40.0 <0.001
PSP, Change from baseline P-value vs placebo*	1.7	2.9 0.509	6.1 0.007	8.3 <0.001
CGI-S, % with at least marked severity P-value vs placebo§#	40.6	31.2 0.140	24.8 0.005	23.1 <0.001

*) Adjusted for multiplicity, §) Unadjusted for multiplicity, #) ANCOVA analysis based on ranks

Figure 7 Change from baseline in total PANSS score by baseline BMI and region in Study PSY-3007. ITT set.



In normal weight patients, treatment effect was significant in all dose groups (25, 100 and 150 mg) increasing with dose. In overweight patients, there were only significant treatment effects in the 100 and 150 mg dose groups, increasing with dose, whereas in obese patients there were no significant treatment effects.

2.5.2.1.2.2. Non inferiority short term studies

Participant flow

This is presented in Tables 13 and 14.

Completion and withdrawal data are given in Tables 13 and 14.

Table 13 Completion and withdrawal data in Study PSY-3006. PP analysis set.

	R092670 (N=389) n (%)	RISPERDAL CONSTA (N=376) n (%)	Total (N=765) n (%)
Completed	328 (84)	319 (85)	647 (85)
Withdrawn	61 (16)	57 (15)	118 (15)
Subject choice(subject withdrew consent)	20 (5)	21 (6)	41 (5)
Lack of efficacy	18 (5)	19 (5)	37 (5)
Lost to follow-up	7 (2)	5 (1)	12 (2)
Adverse event	6 (2)	4 (1)	10 (1)
Death	1 (<1)	0	1 (<1)
Other	9 (2)	8 (2)	17 (2)

Table 14 Completion and withdrawal data in Study PSY-3008. PP analysis set.

	R092670 (N=205) n (%)	RISPERDAL CONSTA (N=208) n (%)	Total (N=413) n (%)
Completed	165(80.5)	185(88.9)	350(84.7)
Withdrawn	40(19.5)	23(11.1)	63(15.3)
Adverse Event	2(1.0)	2(1.0)	4(1.0)
Pregnancy	2(1.0)	0(0.0)	2(0.5)
Protocol Violation	2(1.0)	1(0.5)	3(0.7)
Lack of Efficacy	13(6.3)	7(3.4)	20(4.8)
Lost to Follow-up	7(3.4)	10(4.8)	17(4.1)
Subject Withdrew Consent	9(4.4)	1(0.5)	10(2.4)
Other	5(2.4)	2(1.0)	7(1.7)

Baseline data

These are presented in Tables 15 and 16

Table 15: Diagnosis and psychiatric history at baseline in Study PSY-3006. PP analysis set.

	R092670 (N=389)	RISPERDAL CONSTA (N=376)	Total (N=765)
Schizophrenia type, n (%)			
N	389	376	765
Paranoid (295.30)	351 (90)	346 (92)	697 (91)
Disorganized (295.10)	4 (1)	4 (1)	8 (1)
Catatonic (295.20)	3 (1)	1 (<1)	4 (1)
Undifferentiated (295.90)	22 (6)	15 (4)	37 (5)
Residual (295.60)	9 (2)	10 (3)	19 (2)
Age at diagnosis of schizophrenia (years)			
N	389	376	765
Mean (SD)	27.8 (8.92)	27.9 (9.21)	27.8 (9.06)
Median	26.0	26.0	26.0
Range	(11;57)	(6;58)	(6;58)
Baseline PANSS total score			
N	389	376	765
Mean (SD)	84.9 (11.53)	83.5 (10.92)	84.2 (11.25)
Median	84.0	83.0	83.0
Range	(62;120)	(60;115)	(60;120)
Baseline CGI-S, n (%)			
N	389	376	765
Very mild	0	1 (<1)	1 (<1)
Mild	38 (10)	39 (10)	77 (10)
Moderate	228 (59)	228 (61)	456 (60)
Marked	112 (29)	98 (26)	210 (27)
Severe	11 (3)	10 (3)	21 (3)
Baseline PSP			
N	389	376	765
Mean (SD)	54.3 (12.18)	55.2 (12.08)	54.7 (12.13)
Median	55.0	55.0	55.0
Range	(24;85)	(20;80)	(20;85)
Baseline severity SDS			
N	389	376	765
Mean (SD)	12.6 (4.46)	12.2 (4.44)	12.4 (4.45)
Median	12.0	12.0	12.0
Range	(0;24)	(0;24)	(0;24)
Prior hospitalization[a], n (%)			
N	389	376	765
None	43 (11)	41 (11)	84 (11)
Once	77 (20)	86 (23)	163 (21)
Twice	61 (16)	62 (16)	123 (16)
Three times	56 (14)	56 (15)	112 (15)
Four times or more	152 (39)	131 (35)	283 (37)

[a] Prior hospitalization for psychosis, excluding the current hospitalization.

Table 16: Diagnosis and psychiatric history at baseline in Study PSY-3008. PP analysis set.

	R092670 (N=228)	Risperdal Consta (N=218)	Total (N=446)
Schizophrenia type, n (%)			
N	228	218	446
Disorganized Type	7(3.1)	9(4.1)	16(3.6)
Catatonic Type	0(0.0)	1(0.5)	1(0.2)
Paranoid Type	153(67.1)	145(66.5)	298(66.8)
Residual Type	3(1.3)	0(0.0)	3(0.7)
Undifferentiated Type	65(28.5)	63(28.9)	128(28.7)
Age at diagnosis of schizophrenia (years)			
N	217	206	423
Mean (SD)	26.1(9.40)	25.5(9.52)	25.8(9.45)
Median	23.0	22.0	23.0
Range	(12;61)	(13;54)	(12;61)
Baseline total PANSS			
N	228	218	446
Mean (SD)	82.5(12.24)	84.1(12.66)	83.3(12.46)
Median	80.0	83.0	81.0
Range	(59;115)	(60;120)	(59;120)
Baseline CGI-S, n (%)			
N	226	217	443
Mild	10(4.4)	10(4.6)	20(4.5)
Moderate	52(23.0)	46(21.2)	98(22.1)
Marked	109(48.2)	107(49.3)	216(48.8)
Severe	54(23.9)	53(24.4)	107(24.2)
Extremely severe	1(0.4)	1(0.5)	2(0.5)
Baseline PSP			
N	226	217	443
Mean (SD)	47.3(12.41)	45.3(11.21)	46.3(11.86)
Median	47.0	43.0	45.0
Range	(18; 75)	(21; 78)	(18; 78)

Outcomes and estimation

<u>Study PSY-3006 (non inferiority study versus Risperdal consta)</u>

Table 17 Change from baseline in total PANSS score in Study PSY-3006. PP analysis set.

Parameter: Total PANSS	R092670 (N=389)	Risperdal Consta (N=376)
Baseline		
N	389	376
Mean (SD)	84.9 (11.53)	83.5 (10.92)
Median (Range)	84.0 (62;120)	83.0 (60;115)
End point		
N	389	376
Mean (SD)	66.2 (16.40)	65.6 (15.58)
Median (Range)	65.0 (31;152)	66.0 (32;129)
Change from Baseline		
N	389	376
Mean (SD)	-18.6 (15.45)	-17.9 (14.24)
Median (Range)	-18.0 (-74;75)	-17.0 (-58;50)
Weighted difference (SE)[a,b]		0.4 (1.02)
95% CI		(-1.62;2.38)

Figure 8 Non-inferiority results in Study PSY-3006.

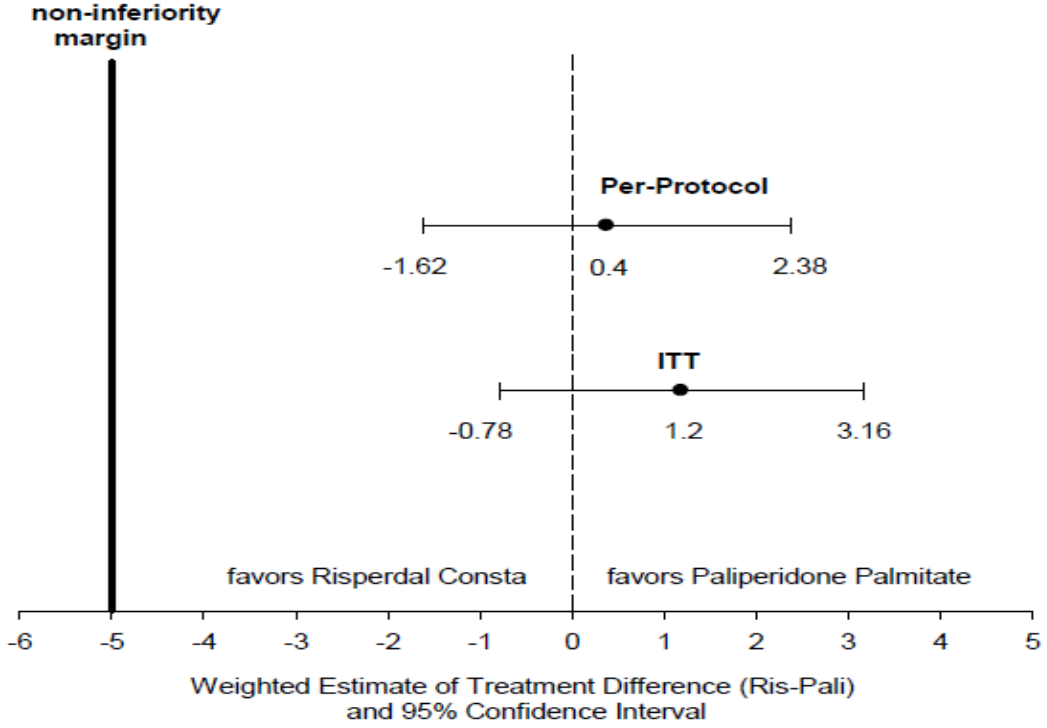


Figure 9 Responder results in Study PSY-3006. Cumulative distribution plot of percent change in total PANSS score. ITT analysis set.

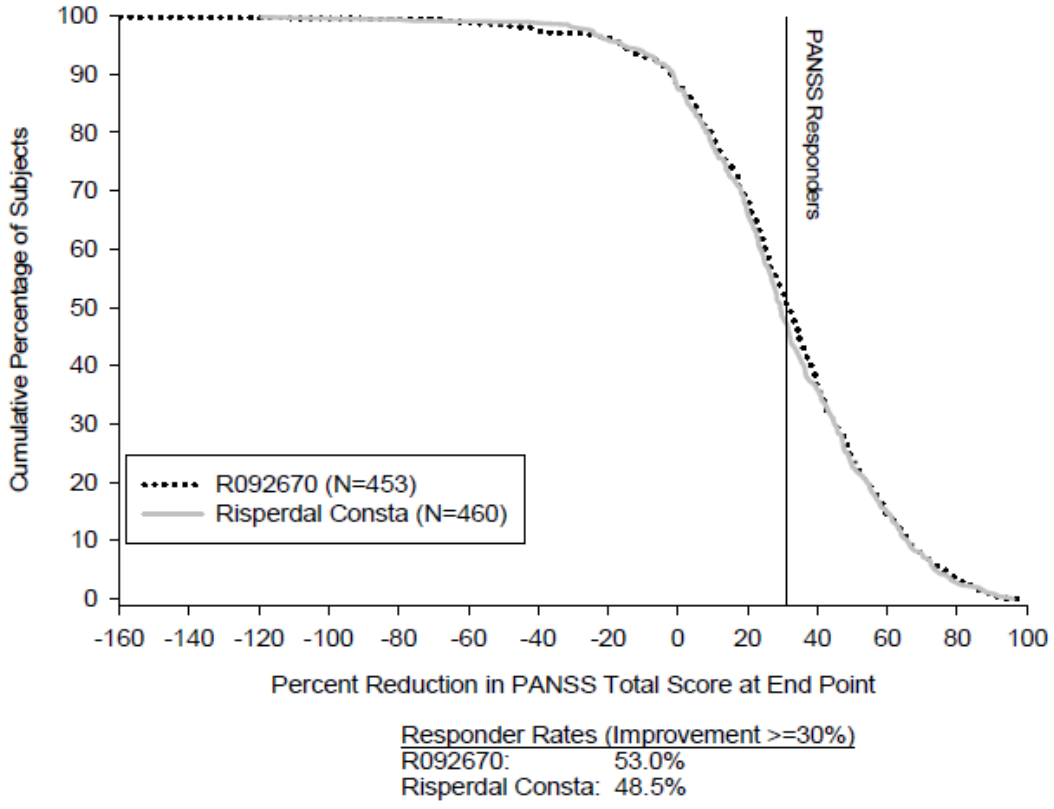


Figure 10 PSP results in Study PSY-3006. Cumulative distribution plot of change in PSP category. ITT analysis set.

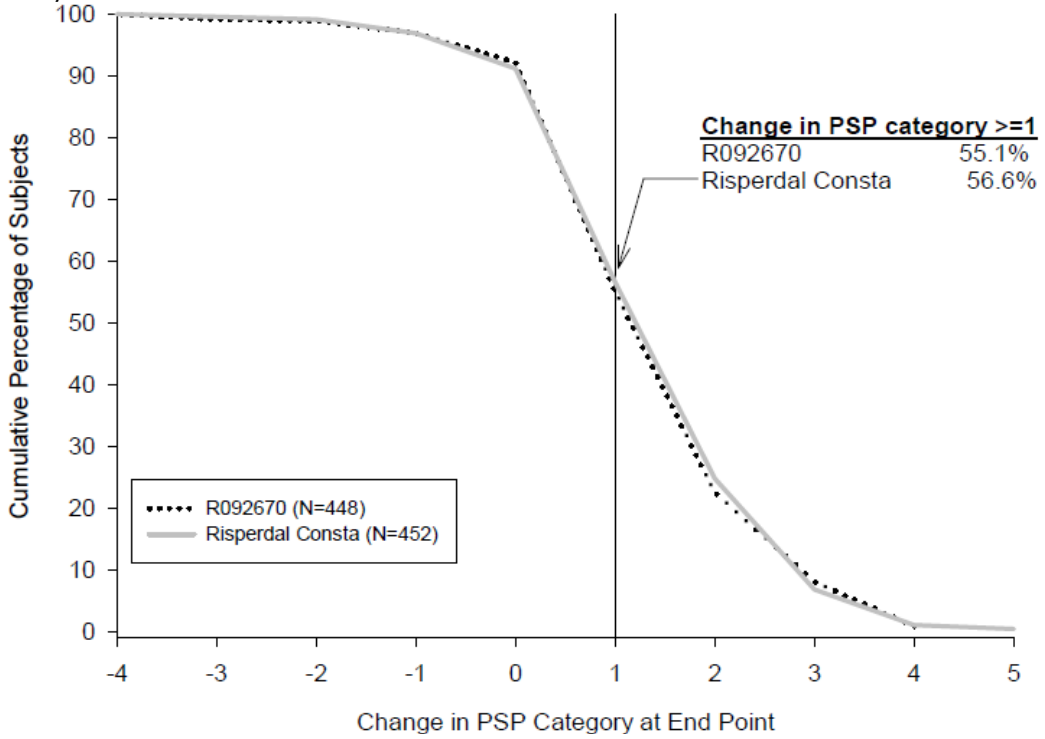


Figure 11 CGI-S results in Study PSY-3006

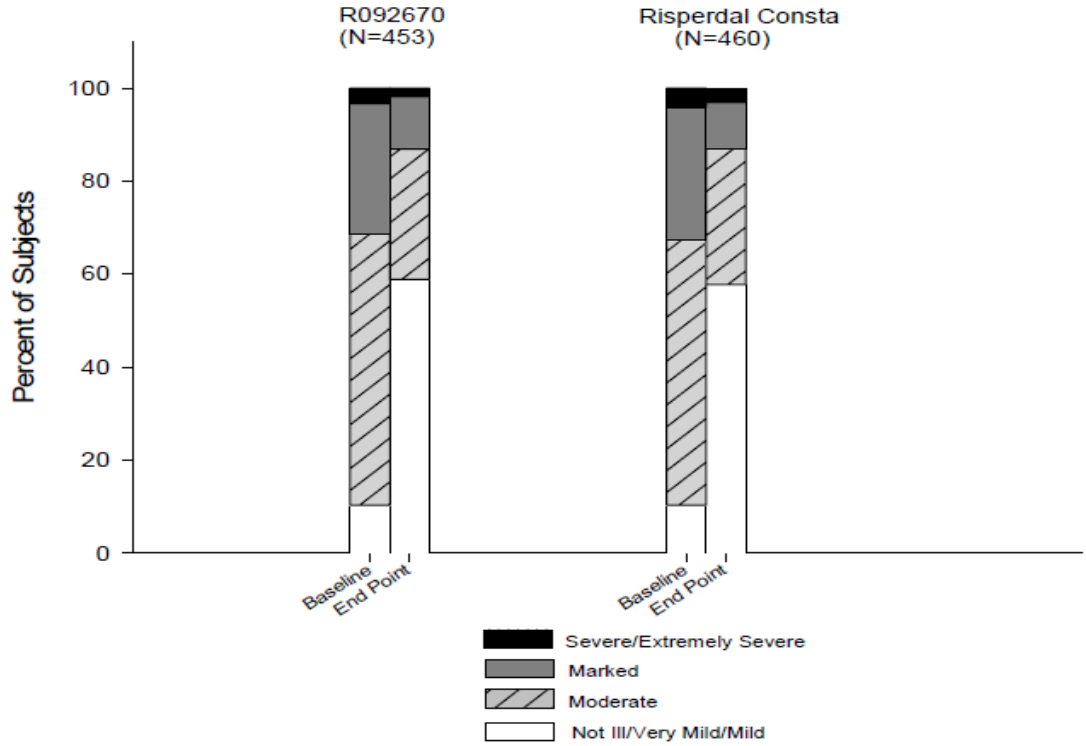
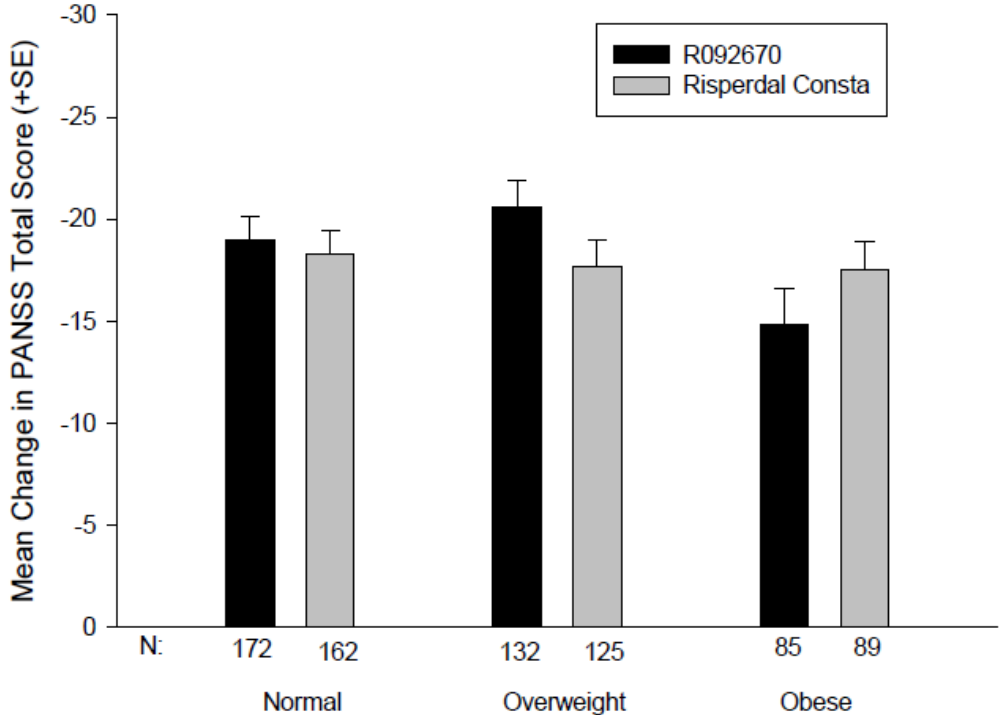


Figure 12 Change from baseline in total PANSS score by baseline BMI in study PSY-3006.



Study PSY-3008

Table 18 Primary and secondary results in Study PSY-3008

Endpoint	R092670 50 mg	Risperdal Consta	Difference (95% CI)
PANSS, Change from baseline PP-set	-23.6	-26.9	-2.3 [-5.20; 0.63]
PANSS, Change from baseline ITT set	-20.9	-25.6	-4.0 [-7.17;-0.89]
Responders (%), ≥30% improvement, PP set	64	75	-11 [2.15; 19.85]
PSP, Change from baseline PP set	16.8	18.6	0.5 [-2.14; 3.12]
CGI-S, % with at least marked severity, PP set	19.0	15.4	3.6 [-3.6; 10.8]

Figure 13 Results of the non-inferiority analyses in Study PSY-3008

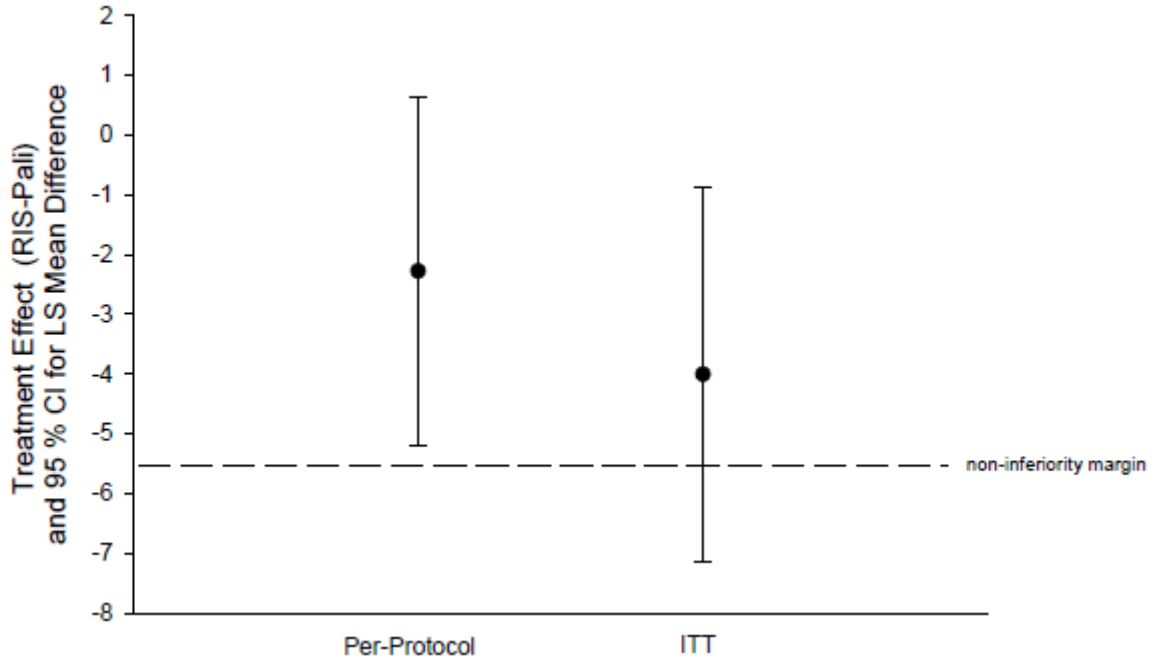
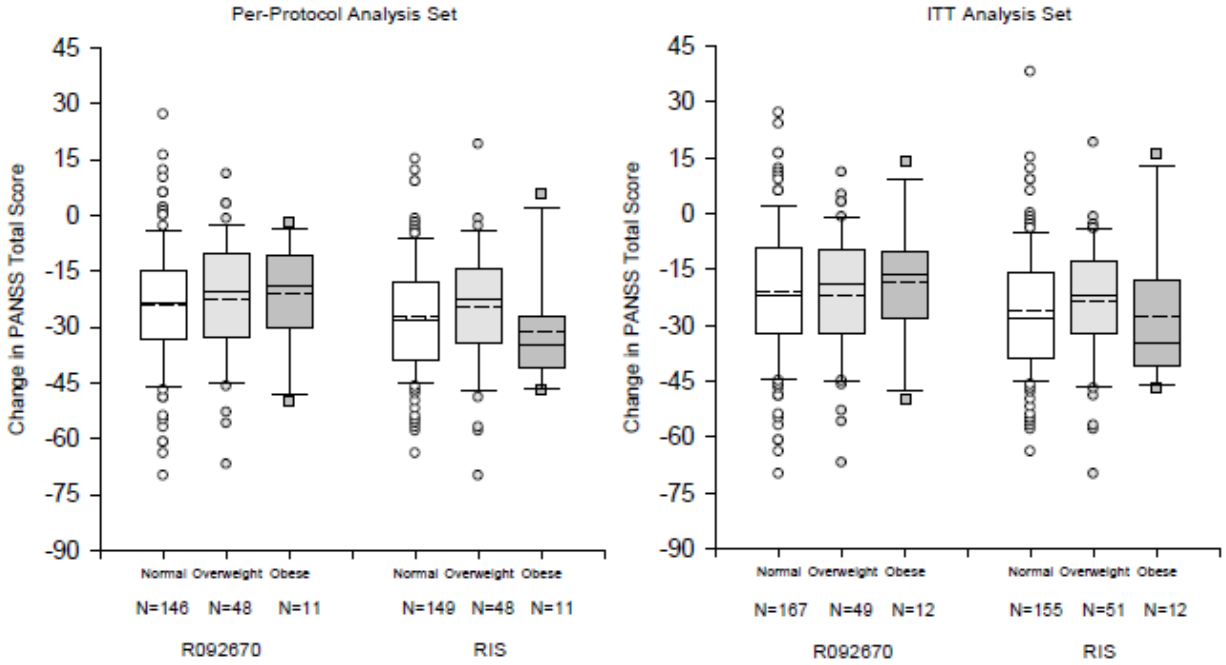


Figure 14 Box.Plots for change from baseline in total PANSS score by baseline BMI in Study PSY-3008.



2.5.2.2. Long term studies

2.5.2.2.1. Methods

The long-term studies were designed as follows:

- PSY-3001 (**relapse prevention study**): a phase III, randomised, double-blind, placebo-controlled, parallel group fixed dose study to evaluate the efficacy and safety of 25, 50 or 100 mg eq of paliperidone palmitate in preventing recurrence in subjects with schizophrenia. This study was extended to a 52 week open label phase. PSY-3001 was conducted in Ukraine, Romania, Russia, South Africa, Taiwan, Korea, Costa Rica, Mexico and the United States.
- PSY-3002 (**non inferiority study versus Risperdal consta**): a phase III, 54 week, randomised, double-blind, active-controlled, parallel group, flexible dose study to evaluate the efficacy and safety of 25, 50, 75 or 100 mg eq of paliperidone palmitate versus 25, 37.5 or 50 mg risperidone long acting injectable in subjects with schizophrenia. PSY-3002 was conducted in Europe, Switzerland, New Zealand and the United States.

Study participants

Main inclusion and and exclusion criteria were similar to the criteria for the short-term studies, with the exception that in study PSY-3001, stable patients could also be included i.e. there was no lower bound for the baseline PANSS score.

In study PSY-3001, additional eligibility criteria for the different phases included the following:

- maintenance phase: subjects had to show tolerance for the treatment and have control of acute symptoms, defined as PANSS total score of equal or less than 75 at week 9.
- double blind recurrence phase: 1) PANSS score equal or less than 75 and 2) scores of equal or less than 4 for PANSS items P1 (delusions), P2 (conceptual disorganisation), P3 (hallucinatory behaviour), P6 (suspiciousness/persecution), P7 (hostility), G8 (uncooperativeness) and G14 (poor impulse control).
- extension phase: subjects who experienced a recurrence, or completed the double blind recurrence phase or who had received at least 1 injection of paliperidone palmitate when enrolment in the study was stopped.

Treatments

In all long term studies, paliperidone palmitate was administered at day 1 and 8 and every 4 weeks thereafter, exclusively in a gluteal muscle.

Study PSY-3001

The study consisted of 5 phases: a screening/wash out/tolerability period (up to 7 days), a 9 week open-label transition phase, a 24 week open label maintenance, a placebo controlled recurrence prevention phase of variable duration and an optional 52 week open label extension.

The 9 week open label transition phase allowed for switching from oral or long acting injectable antipsychotics to paliperidone palmitate and included 2 complete 4 week intervals between

administrations of paliperidone palmitate. The treatment dose was flexible (25mg, 50 mg or 100 mg eq) based on clinical need.

The 24 week open label maintenance phase allowed for identification of subjects who maintained control of their symptoms on a stable dosing regimen. In the first 12 weeks, the treatment dose was flexible (25mg, 50 mg or 100 mg eq) based on clinical need. In the last 12 weeks of the phase, no further adjustments of the dose were allowed.

The double blind recurrence phase had a variable duration due to a randomized withdrawal design, ie. patients remained in this phase until they experienced a recurrence event or met discontinuation/withdrawal criteria or predefined study conclusion criteria. Subjects were randomly assigned in a 1:1 ratio to receive either a fixed dose of paliperidone palmitate (starting at the final dose used in the maintenance phase) or placebo.

In the 52 week open label extension, subjects received paliperidone palmitate every 4 weeks. Oral supplementation was allowed during the first 8 weeks given it was not possible to administer an initial dose for placebo treated subject without breaking the blinding.

Study PSY-3002

The study consisted of a screening/wash out/tolerability period (up to 7 days) and a 53 week double blind treatment period. Subjects were randomly assigned in a 1:1 ratio to either a flexible dose of paliperidone palmitate (25,50,75 or 100 mg eq) or long acting injectable risperidone (25, 37.5 or 50 mg), starting in both groups at 25 mg dose.

Outcomes/endpoints

In study PSY-3001, the primary endpoint was time to first relapse, with relapse defined as one of the following:

- Psychiatric hospitalization (involuntary or voluntary admission to a psychiatric hospital for decompensation of the subject's schizophrenic symptoms), or
- For PANSS: increase of 25% in the total PANSS score from randomization for 2 consecutive assessments separated by 3 to 7 days if the score at randomization was >40, or a 10-point increase in the total PANSS score from randomization for 2 consecutive assessments separated by 3 to 7 days if the score at randomization was ≤40, or
- Deliberate self-injury and/or violent behaviour resulting in suicide or in clinically significant injury to the subject or another person or property damage, or
- Suicidal or homicidal ideation and aggressive behaviour that was clinically significant (in frequency and severity) in the investigator's judgment, or
- For PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behaviour), P6 (suspiciousness/persecution), P7 (hostility) or G8 (uncooperativeness): a score ≥5 after randomization for 2 consecutive assessments separated by 3 to 7 days on any of the above PANSS items if the maximum score for the above PANSS items was ≤ 3 at randomization, or a score ≥6 after randomization for 2 consecutive assessments separated by 3 to 7 days on any of the above PANSS items if the maximum score for the above PANSS items was 4 at randomization.

In study PSY-3002, the primary endpoint was the same as in the short term studies: change from baseline in PANSS total score.

Sample size

In study PSY-3001, the sample size calculation was 90% power to detect a relative risk for relapse of 0.56 at a two-sided significance level of 0.05. In study PSY-3002, the non-inferiority margin was set to a difference of 5 points. The power was specified to 80 % at a two-sided significance level of 0.05.

Randomisation

Eligible subjects were randomly assigned prior entering the double blind recurrence phase (study PSY-3001) or at baseline (study PSY-3002) in a specified ratio and according to a computer-generated randomisation schedule prepared by the sponsor prior to the study. Randomisation was balanced by using permuted blocks and was stratified by center. Central randomisation was used via interactive voice response system (IVRS).

Blinding (masking)

Placebo and active drug differed in appearance.. To keep the blinding, double dummy technique was applied (when applicable) and treatment was administered by a dedicated study staff who was not allowed to take part in any other study activities or study related discussions with other study personnel. Prolactin levels were not available to investigator or the sponsor during the study period.

Statistical methods

The primary endpoint in study PSY-3001 was analysed using the log-rank test and the survival curves were estimated with the Kaplan-Meier method. Alternative analyses were performed with Cox proportional hazards regression analysis. An interim analysis was also performed and defined as the date when the 68th recurrence event was observed (50% of the planned recurrence events).

In study PSY-3002, the statistical approach for primary and secondary analyses was similar to the methods used in the short-term studies.

2.5.2.2.2. Results

Participation flow

This is presented in Figure 15 and Table 19.

Figure 15 Patient disposition in Study PSY-3001

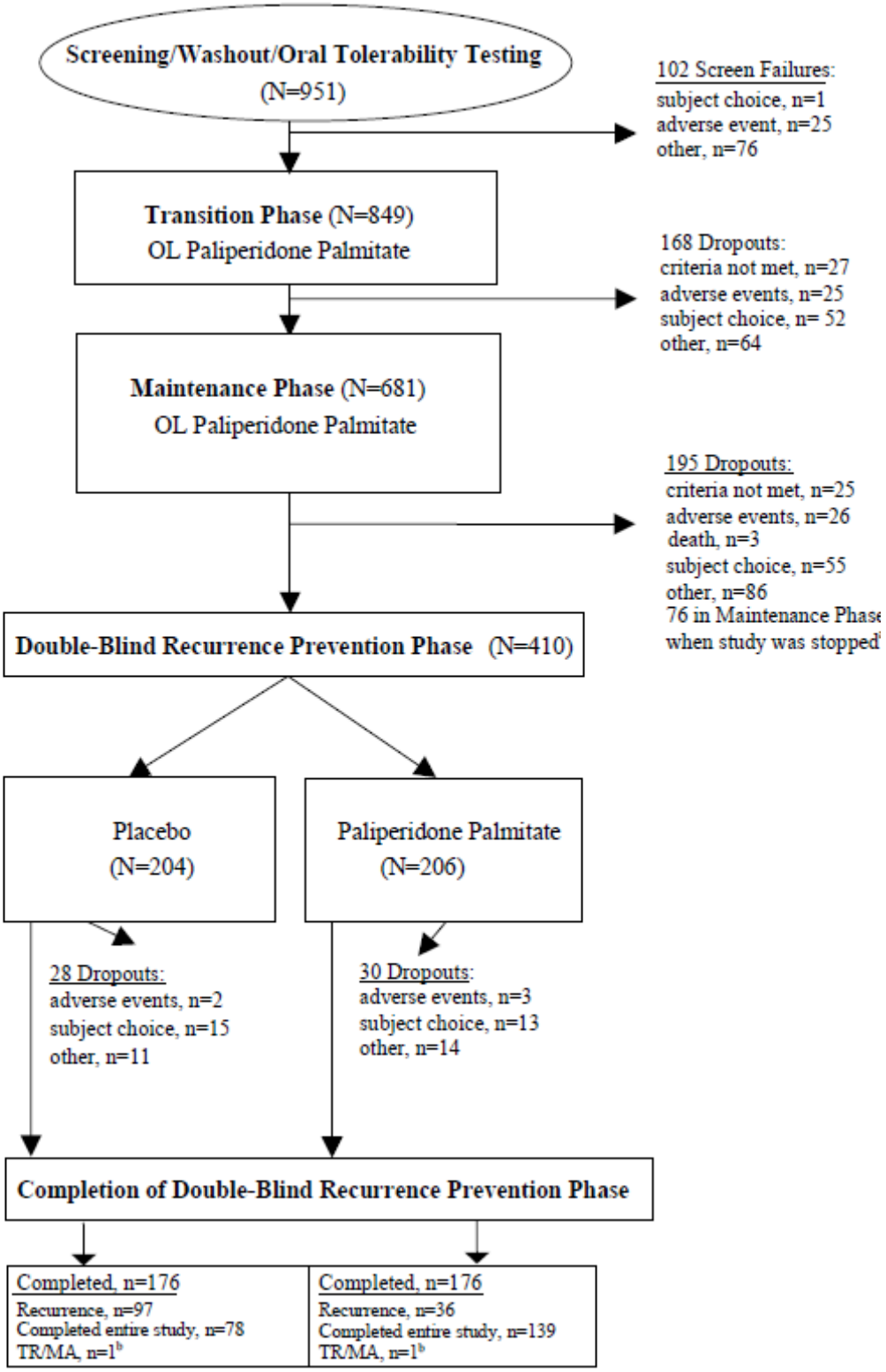


Table 19 Completion and withdrawal in Study PSY-3002. All randomised patients.

	R092670 (N=379) n (%)	RISPERDAL CONSTA (N=370) n (%)	Total (N=749) n (%)
Completed	155 (41)	184 (50)	339 (45)
Withdrawn	224 (59)	186 (50)	410 (55)
Lack of efficacy	95 (25)	56 (15)	151 (20)
Subject choice (subject withdrew consent)	55 (15)	62 (17)	117 (16)
Adverse event	29 (8)	25 (7)	54 (7)
Lost to follow-up	13 (3)	11 (3)	24 (3)
Pregnancy	1 (<1)	1 (<1)	2 (<1)
Death	2 (1)	0	2 (<1)
Other	29 (8)	31 (8)	60 (8)

Baseline data

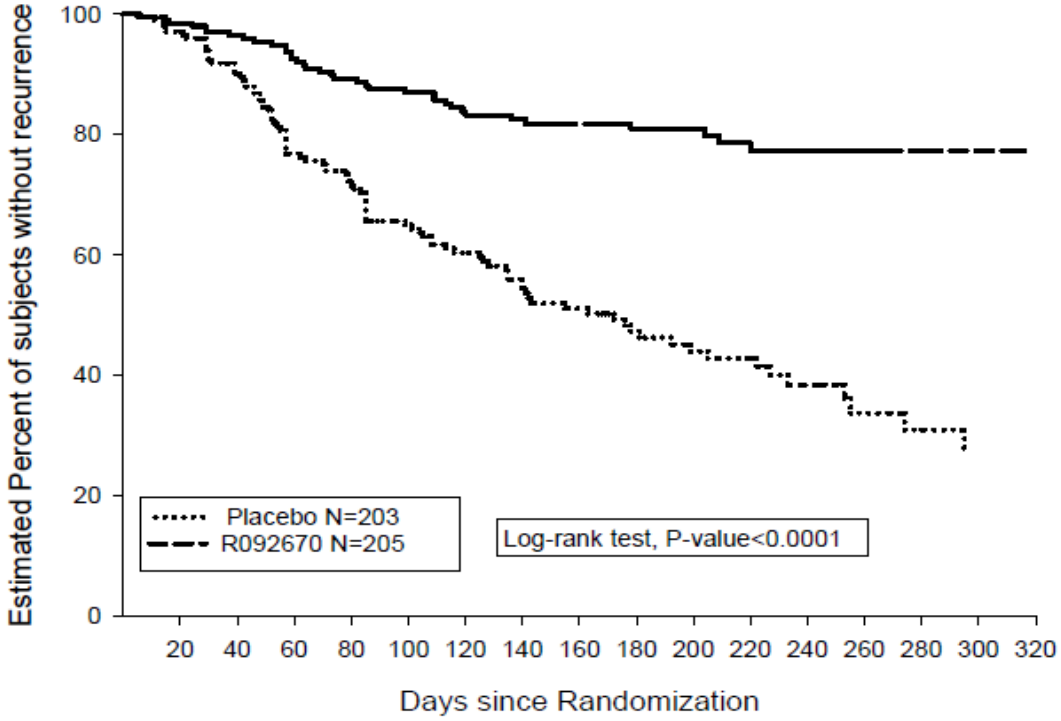
There were no major imbalances between treatment groups with respect to demographic and baseline characteristics. In Study PSY-3001 EU patients were exclusively enrolled in Romania while Western as well as Eastern Europe was well represented in Study PSY-3002.

The dominating schizophrenia subtype was paranoid (about 80% in both studies) According to the CGI-S ratings severity less in Study PSY-3002 (36% with at least marked severity) compared to Study PSY-3001 (54%). On the other hand more patients had been hospitalised three times or more in Study PSY-3002 (55%) compared to Study PSY-3001 (46%) and the average baseline PANSS score was higher in Study PSY-3002.

Outcomes and estimation

Study PSY-3001 (relapse prevention study)

Figure 16 Results of the final primary analysis in Study PSY-3001. Time to relapse. ITT analysis set.



Number of Subjects at Risk																		
Time	0	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	320	
Placebo	203	192	163	136	121	101	84	71	58	47	37	34	22	13	9	6	6	
R092670	205	194	180	168	158	146	130	120	106	89	72	61	40	22	15	14	11	

Table 20 Cause for relapse in Study PSY-3001.

Type of Recurrence Reason	Placebo (N=203) N	R092670 (N=205) n
Psychiatric hospitalization	16	5
Psychiatric hospitalization	16	5
PANSS	85	32
Increase of 25% in total PANSS score	73	29
10 point increase in total PANSS score	12	3
Deliberate self-injury, violent behavior	4	1
Deliberate self-injury, violent behavior	4	1
Suicidal or homicidal ideation	5	1
Suicidal or homicidal ideation	5	1
PANSS items p1,p2,p3,p6,p7,g8	24	12
Score ≥5 for 2 days	24	12

Relapses prevention was similar in the two dominating regions US and Eastern Europe. Neither was there any difference in effect depending on baseline BMI. Statistical significance was reported for normal, overweight as well obese patients. At double-blind end point, there were more subjects in the paliperidone palmitate group (75%, 152/203) than in the placebo group (56%, 114/202) with severity scores of "mild", "very mild", or "not ill". Ratings of "marked" or "severe" (i.e., rating of ≥5) were reported for 29 subjects in the placebo group compared with 10 in the paliperidone palmitate group. Other secondary results are summarised in Table 21.

Table 21 Secondary results in Study PSY-3001.

Endpoint	**R092670 50 mg**	**Placebo**	**Difference (95% CI)**
PANSS, Change from baseline ITT final set	2.5	11.1	-8.6 [-11.41;-5.70]
PSP, Change from baseline ITT final set	-1.5	-7.2	5.3 [2.99; 7.67]

Study PSY-3002 (non inferiority study versus Risperdal consta)

Table 22 Primary and secondary results in Study PSY-3002.

Endpoint	**R092670 50 mg**	**Risperdal Consta**	**Difference (95% CI)**
PANSS, Change from baseline PP-set	-11.6	-14.4	-2.6 [-5.84; 0.61]
PANSS, Change from baseline ITT set	-9.5	-13.0	-3.8 [-6.96;-0.74]
Responders (%), ≥30% improvement, ITT set	44.3	54.4	-11.1 [3.51; 18.59]
PSP, Change from baseline PP set	3.7	5.2	1.7 [-0.61; 3.97]
CGI-S, % with at least marked severity, PP set	19.0	15.4	6.7 [-0.3; 13.7]

Figure 17 Non-inferiority results in Study PSY-3002.

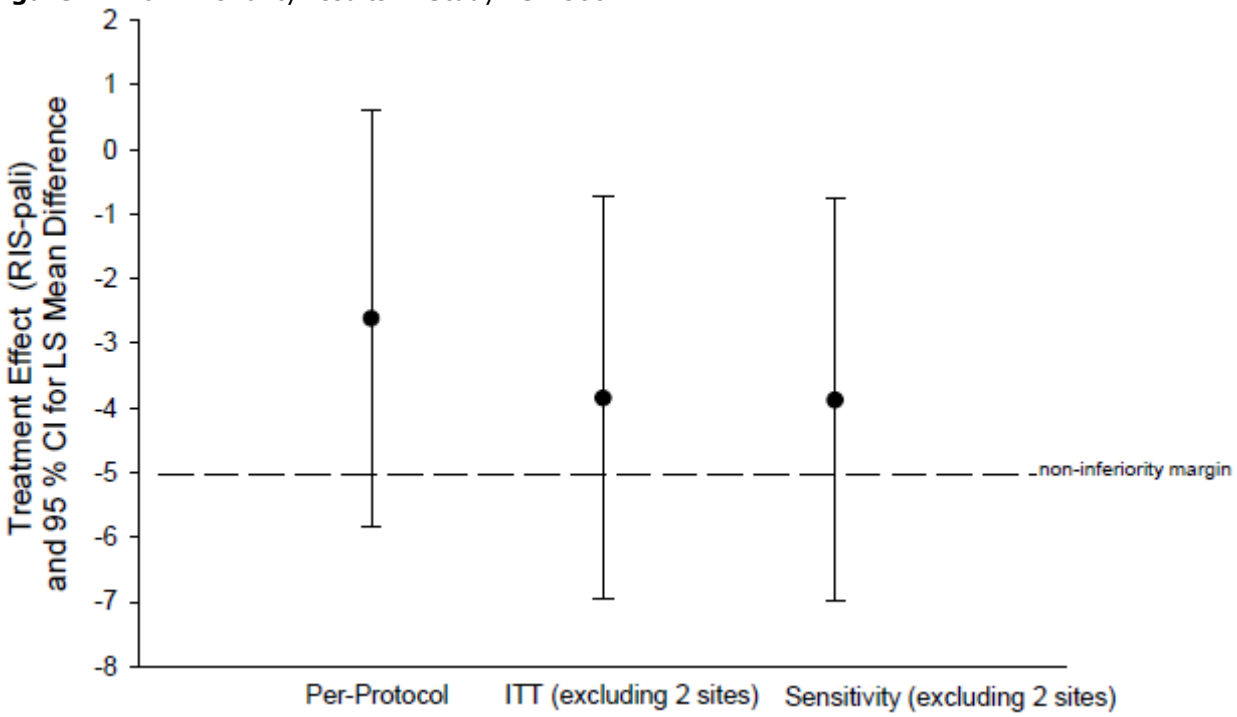


Figure 18 Change from baseline in total PANSS score by region in Study PSY-3002

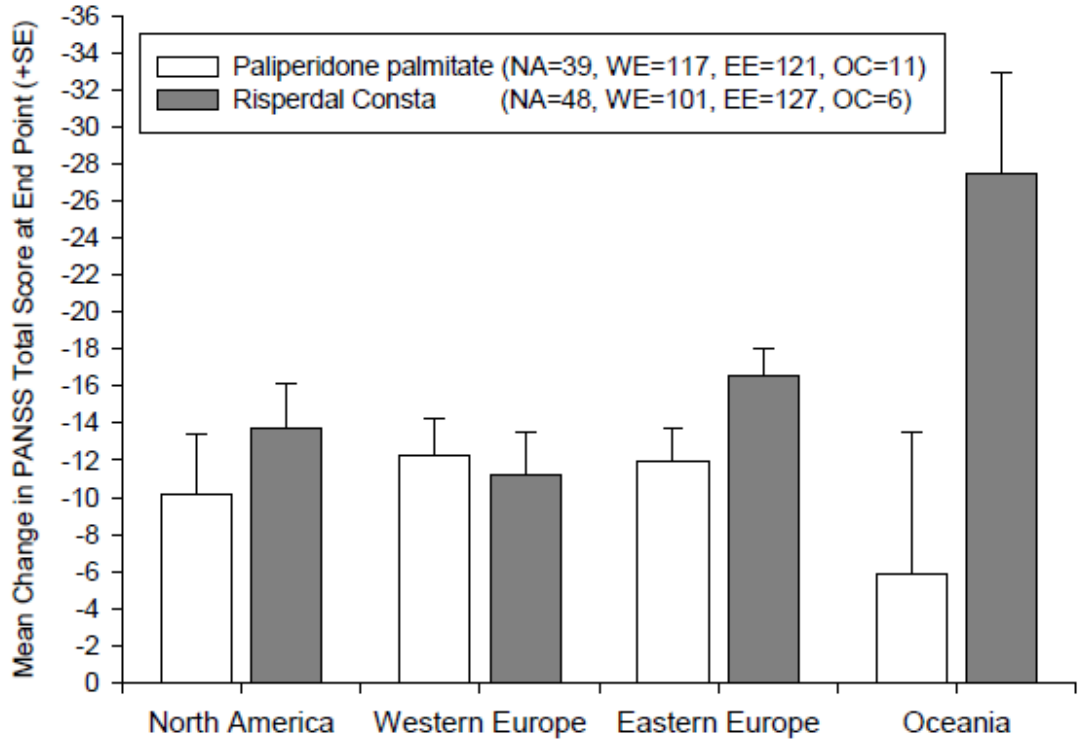
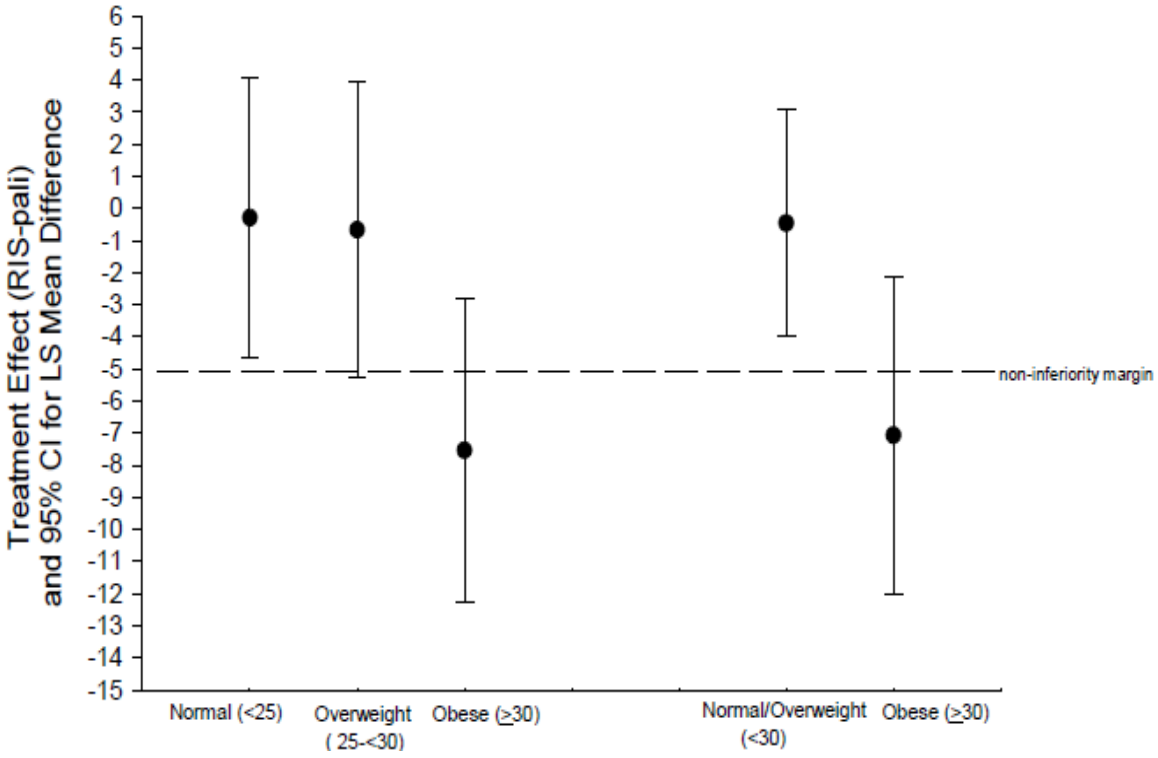


Figure 19 Non-inferiority results by baseline BMI in Study PSY-3002



2.5.2.3. Ancillary analyses

In the short-term placebo controlled studies, the magnitude of effect varied across doses and age groups (probably due to small patient numbers) but there was no consistent pattern suggesting that any particular age groups should benefit more or less from paliperidone palmitate treatment. Similarly, there was no consistent pattern in the non-inferiority studies favouring any of the active treatments in a particular age subgroup. In total, there were only 17 patients above 65 years of age in the short-term studies.

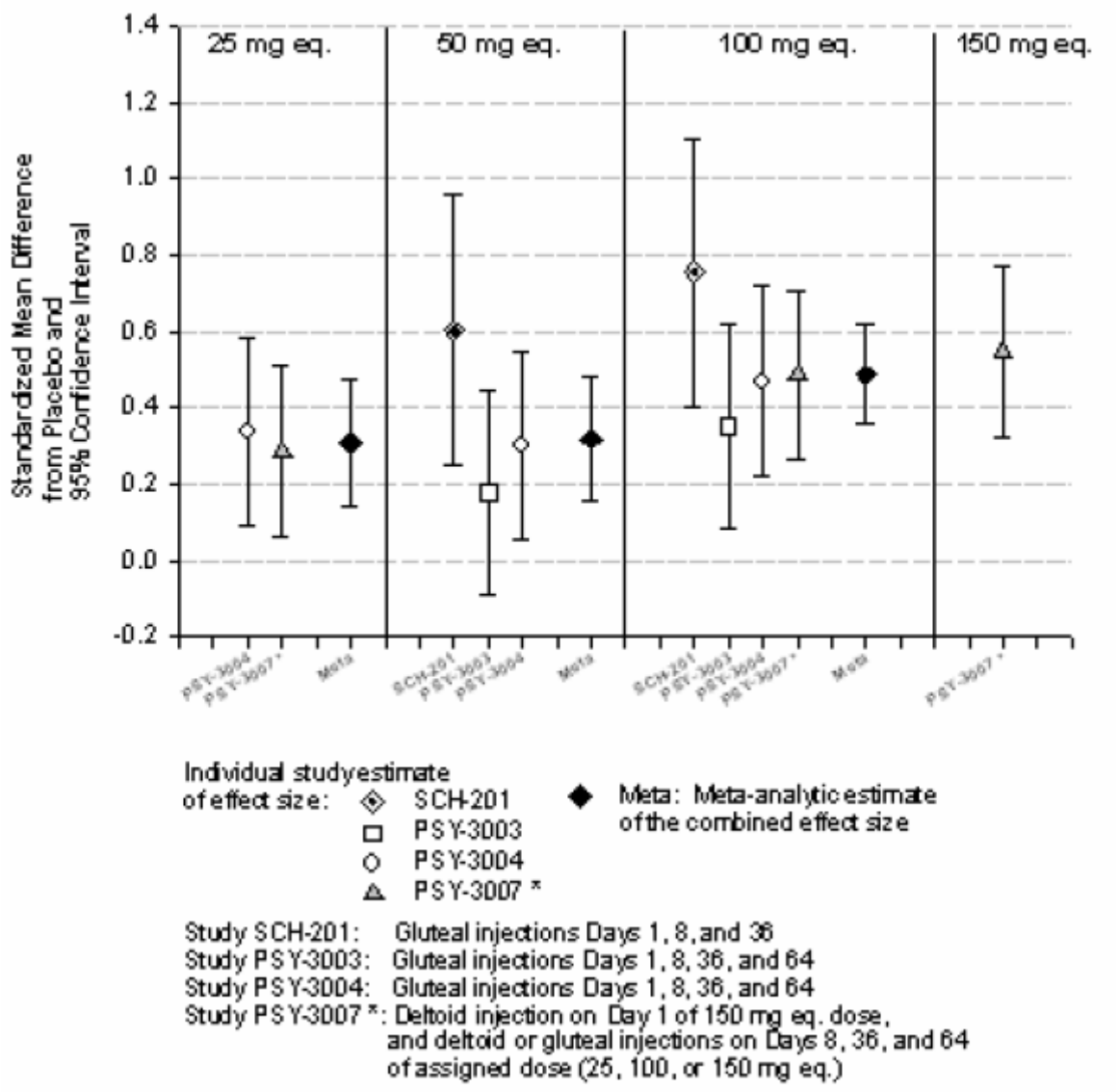
In the short-term placebo controlled studies, effect of race on paliperidone palmitate efficacy was observed. However, no differences were observed in non inferiority studies and the number of patients analysed was small.

Overall, there were no major differences on efficacy between patients with a baseline PANSS score below and above the median value.

2.5.2.4. Analysis performed across trials (pooled analyses and meta-analysis)

A pooled analysis across all placebo controlled short term studies was performed to support the dose-response relationship for paliperidone palmitate (see Figure 20).

Figure 20 Standardised differences of total PANSS score in the short-term placebo controlled studies. Pooled analyses.



2.5.2.5. Efficacy data and additional analyses

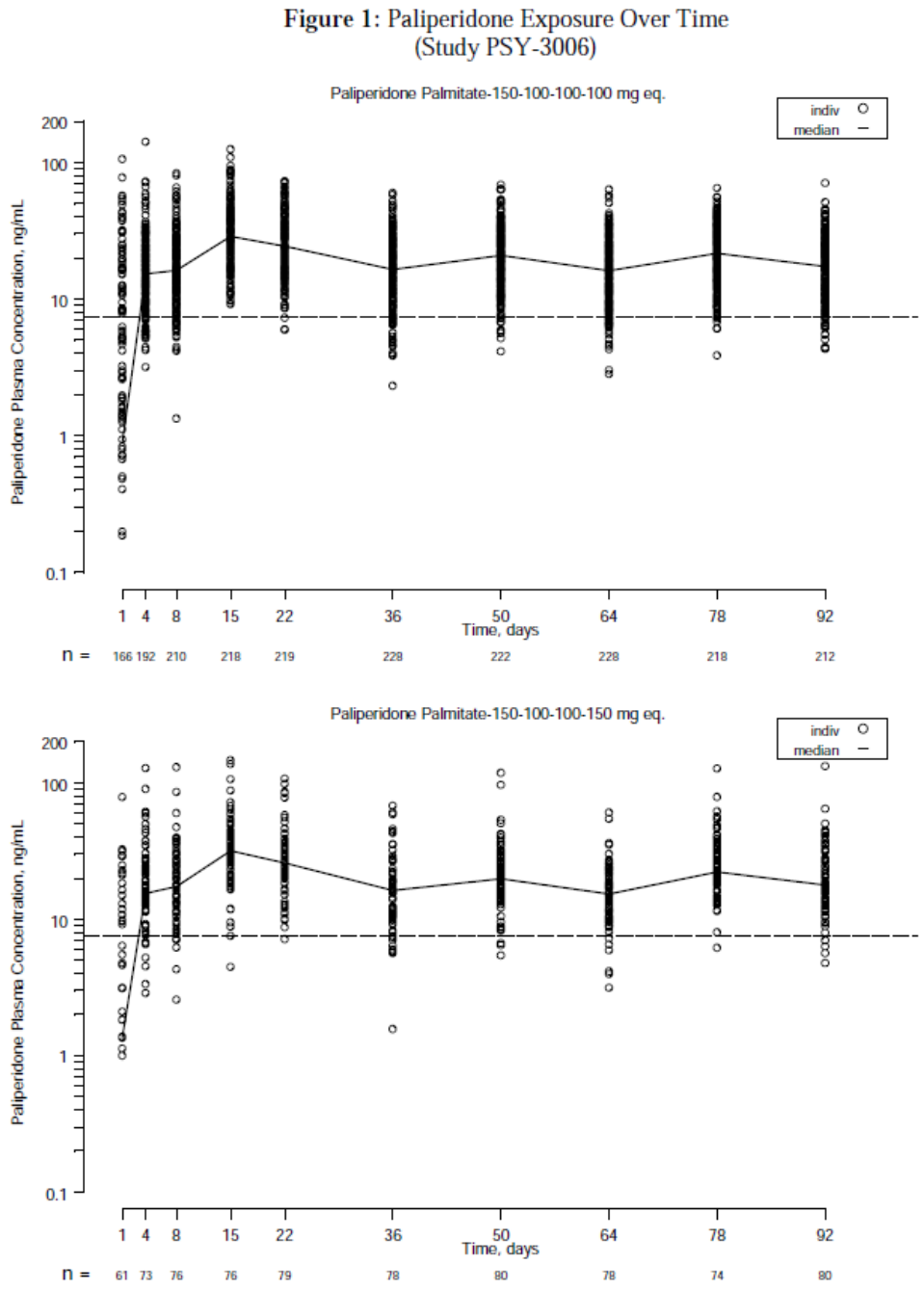
Onset of efficacy

Exposure to paliperidone

Figure 25 presents the 2 most common dosing regimens used in Study PSY-3006 (paliperidone palmitate injections of 150 mg eq. on Day 1, followed by 100 mg eq. on Day 8, and then either 2 monthly injections of 100 mg eq. or of 100 mg eq. and 150 mg eq.). The graphs show that the majority of subjects receiving the recommended initiation regimen achieved a therapeutic concentration of paliperidone (>7.5 ng/mL) by Day 4. Similar results are presented in PSY 3007 (Figure 26) A paliperidone concentration of 7.5 ng/mL was associated with a central D2-receptor occupancy of approximately 60%, which is typically considered as the threshold for potential efficacy

(Pani 2007[3]).There was no evidence of a rapid decline in paliperidone plasma levels between Day 1 and Day 8, in contrast with the exposure changes observed in earlier studies (ie, SCH-201).

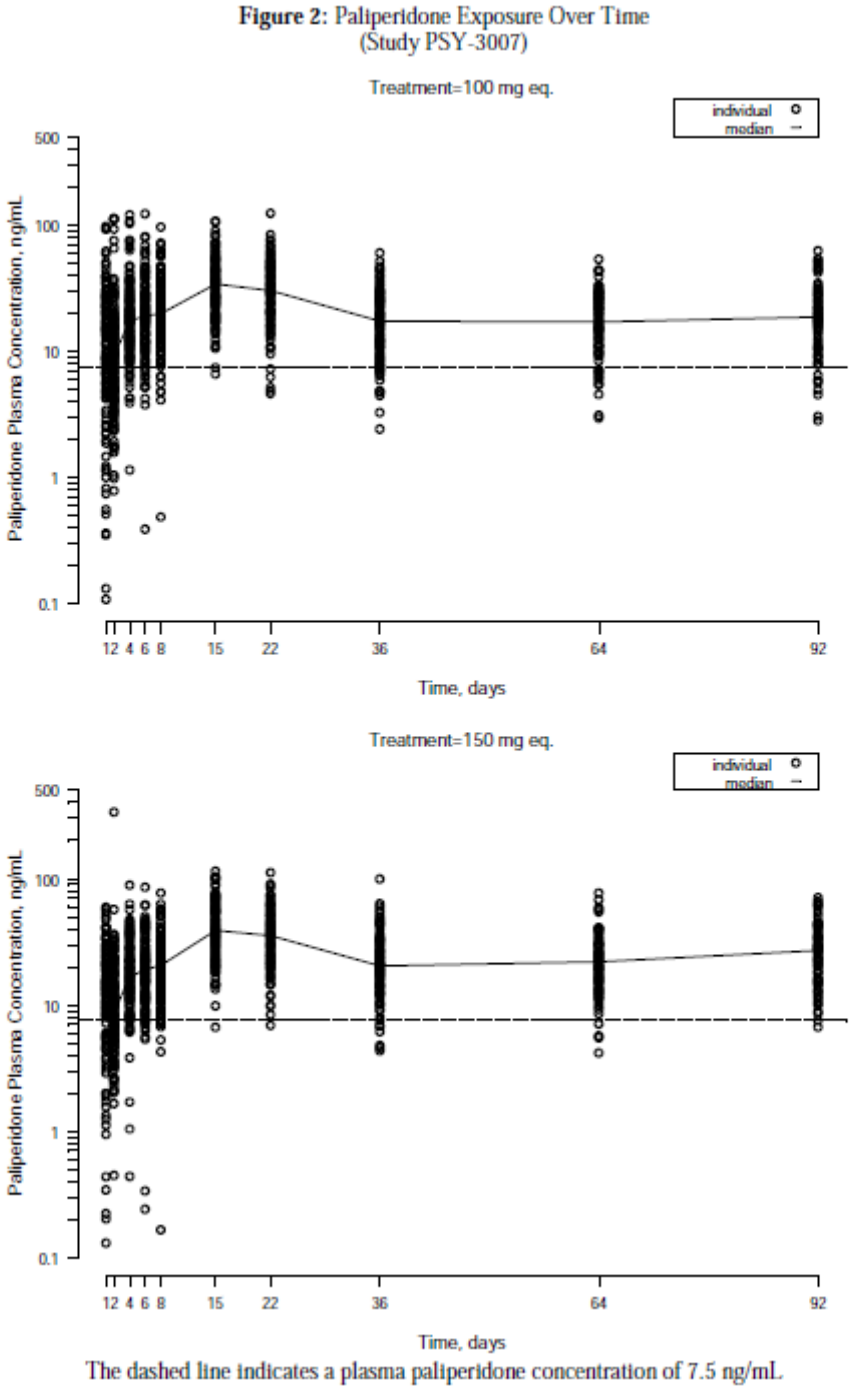
Figure 21



The dashed line indicates a plasma paliperidone concentration of 7.5 ng/mL

[3] Pani L, Pira L, Marchese G (2007). Antipsychotic efficacy: Relationship to optimal D2-receptor occupancy. European Psychiatry 22: 267-275.

Figure 22



Primary endpoint – Change from baseline in PANSS total score

For studies in patients with schizophrenia, the earliest measurement of onset of efficacy has been variously defined. Both a large non-placebo-controlled meta-analysis of oral antipsychotic agents (Agid 2003[4]) and a pooled analysis of 7 double-blind placebo-controlled studies of amisulpride (Leucht 2005[5]) demonstrated incremental improvements over baseline in PANSS total score or define BPRS

4 Agid O, Kapur S, Arenovich T, Zipursky RB (2003) Delayed-onset hypothesis of antipsychotic action: a hypothesis tested and rejected. Arch Gen Psychiatry 60:1228-1235.

5 Leucht S, Busch R, Hamann J, Kissling W, Kane JM (2005); Early-onset hypothesis of antipsychotic drug action: a hypothesis tested, confirmed and extended. Biol Psychiatry 57: 1543-1549.

within the first 1 to 2 weeks of therapy. These data have been generally viewed as supporting an early onset of effect for oral agents (Agid 2006[6]).

In studies SCH-303, SCH-304, and SCH-305 submitted as part of the application for oral paliperidone (Invega), onset of therapeutic effect was assessed by determining *the earliest time point at which active treatment demonstrated a statistically significant improvement over placebo, maintained at all subsequent time points, for the change from baseline in PANSS total score*. Based on the mean change from baseline to each visit for PANSS total score, statistically significant differences compared to placebo were first observed on Day 4 for the paliperidone PR 3 mg, 6 mg, 9 mg, and 12 mg groups, and on Day 8 for the 15 mg group, and these improvements were maintained for the duration of the 6-week double-blind phase. In study PSY-3007 with paliperidone palmitate i.m, using the same definition of onset of efficacy, statistically significantly greater improvement over placebo on mean PANSS total score was observed some days later at Day 8 (change from baseline: -8.21 [0.87] versus -5.79 [1.20], p=0.027). Although not statistically significant, improvement in PANSS total score over placebo was noted as early as Day 4. Numerically greater improvements in both the Clinical Global Improvement-Severity CGI-S and PSP scores were noted on Day 8 onwards as compared to placebo (see Table 23).

Table 23

Table 1: Least-Squares Mean Change From Baseline for Primary and Secondary Efficacy Variables During the First 36 Days of Treatment - LOCF (Study R092670-PSY-3007: Intent-to-Treat Analysis Set)

Visit Day	Paliperidone Palmitate (N=476)	Placebo (N=160)
PANSS Total Score		
Baseline Mean (SD)	87.2 (11.50)	86.8 (10.31)
D4 LS Mean Change (95% CI)	-4.0 (-5.32 to -2.74)	-3.0 (-4.83 to -1.26)
D8 LS Mean Change (95% CI)	-8.2 (-9.92 to -6.50)	-5.8 (-8.14 to -3.44)
D22 LS Mean Change (95% CI)	-10.3 (-12.29 to -8.31)	-5.4 (-8.16 to -2.68)
D36 LS Mean Change (95% CI)	-12.3 (-14.43 to -10.16)	-6.5 (-9.39 to -3.51)
CGI-S Score		
Baseline Mean (SD)	4.5 (0.65)	4.6 (0.63)
D4 LS Mean Change (95% CI)	-0.2 (-0.28 to -0.12)	-0.2 (-0.29 to -0.07)
D8 LS Mean Change (95% CI)	-0.5 (-0.61 to -0.41)	-0.4 (-0.55 to -0.27)
D22 LS Mean Change (95% CI)	-0.7 (-0.81 to -0.58)	-0.4 (-0.59 to -0.28)
D36 LS Mean Change (95% CI)	-0.8 (-0.92 to -0.67)	-0.5 (-0.68 to -0.34)
PSP		
Baseline Mean (SD)	49.4 (12.67)	49.6 (12.29)
D8 LS Mean Change (95% CI)	6.1 (4.76 to 7.53)	5.0 (3.07 to 6.87)
D22 LS Mean Change (95% CI)	7.3 (5.78 to 8.81)	5.2 (3.10 to 7.26)
D36 LS Mean Change (95% CI)	8.5 (6.89 to 10.14)	6.6 (4.33 to 8.78)

Note: Based on analysis of covariance (ANCOVA) model with treatment and country as factors, and baseline value as a covariate.
Note: Negative change in score indicates improvement for PANSS and CGI-S; positive change in score indicates improvement for PSP.

Secondary endpoint – Responder rate

In studies PSY-3007 and -3006, onset of therapeutic effect was, alternatively, defined as *the time point at which a significant separation from placebo is detected with respect to responder rate.*

[6] Agid O, Seeman P, Kapur S (2006) The "delayed onset" of antipsychotic action — an idea whose time has come and gone J Psychiatry Neurosci 31(2):93-100

In study PSY-3007, paliperidone palmitate (150 mg eq. on Day 1, followed by 25, 50, or 150 mg eq. on Days 8, 36 and 64) was associated with significantly more responders than placebo at Days 22 ($p \leq 0.05$) and 36 ($p \leq 0.036$) where a response was defined as a ≥ 20% or ≥ 30% improvement in PANSS total score, respectively. Regardless of the criteria for response, it is noteworthy that at every time point, beginning at the earliest post-treatment assessment (Day 4), there was a numerically higher responder rate in each of the paliperidone palmitate treatment groups compared to placebo (8.3 versus 5.2 %).

In study PSY-3006, a numerically higher responder rate (defined as a decrease in PANSS total score of at least 30%) was detected at every time point, beginning as early as Day 4 (3.1 versus 1.5%), for paliperidone palmitate when compared with Risperdal consta. There was no difference between the paliperidone palmitate and Risperdal consta treatment groups with regard to the LS mean change from baseline in PANSS total score during the first 36 days of treatment; the 95% confidence intervals (CIs) for the 2 treatment groups overlapped at each time point. Furthermore, during the first 36 days of treatment, the mean changes from baseline for the secondary efficacy variables (CGI-S and PSP scores) were similar for the paliperidone palmitate and Risperdal consta groups (Table 24). No statistical difference between paliperidone palmitate and Risperdal consta (requiring oral supplementation for the first 3 weeks) treatment groups were observed with regard to change from baseline in PANSS total score during the first 36 days of treatment, suggesting that oral supplementation was not required for paliperidone palmitate.

Table 24

Table 2: Least-Squares Mean Change From Baseline for Primary and Secondary Efficacy Variables During the First 36 Days of Treatment - LOCF (Study R092670-PSY-3006: Per Protocol Analysis Set)

Visit Day	Paliperidone Palmitate (N=389)	RISPERDAL CONSTA (N=376)
PANSS Total Score		
Baseline Mean (SD)	84.9 (11.53)	83.5 (10.92)
D4 LS Mean Change (95% CI)	-2.8 (-3.48 to -2.12)	-2.3 (-3.01 to -1.60)
D15 LS Mean Change (95% CI)	-7.3 (-8.52 to -5.99)	-6.9 (-8.22 to -5.59)
D22 LS Mean Change (95% CI)	-11.8 (-13.39 to -10.30)	-11.6 (-13.24 to -10.03)
D36 LS Mean Change (95% CI)	-14.0 (-15.87 to -12.15)	-13.2 (-15.12 to -11.24)
CGI-S Score		
Baseline Mean (SD)	4.2 (0.66)	4.2 (0.66)
D4 LS Mean Change (95% CI)	-0.0 (-0.07 to 0.01)	-0.0 (-0.08 to 0.01)
D15 LS Mean Change (95% CI)	-0.3 (-0.40 to -0.23)	-0.3 (-0.39 to -0.22)
D22 LS Mean Change (95% CI)	-0.5 (-0.56 to -0.37)	-0.5 (-0.58 to -0.38)
D36 LS Mean Change (95% CI)	-0.6 (-0.73 to -0.50)	-0.6 (-0.68 to -0.44)
PSP		
Baseline Mean (SD)	54.3 (12.18)	55.2 (12.08)
D15 LS Mean Change (95% CI)	3.0 (2.07 to 3.94)	3.5 (2.51 to 4.47)
D36 LS Mean Change (95% CI)	5.6 (4.26 to 6.92)	5.6 (4.20 to 6.98)

Note: Based on analysis of covariance (ANCOVA) model with treatment and country as factors, and baseline value as a covariate.
Note: Negative change in score indicates improvement for PANSS and CGI-S; positive change in score indicates improvement for PSP.

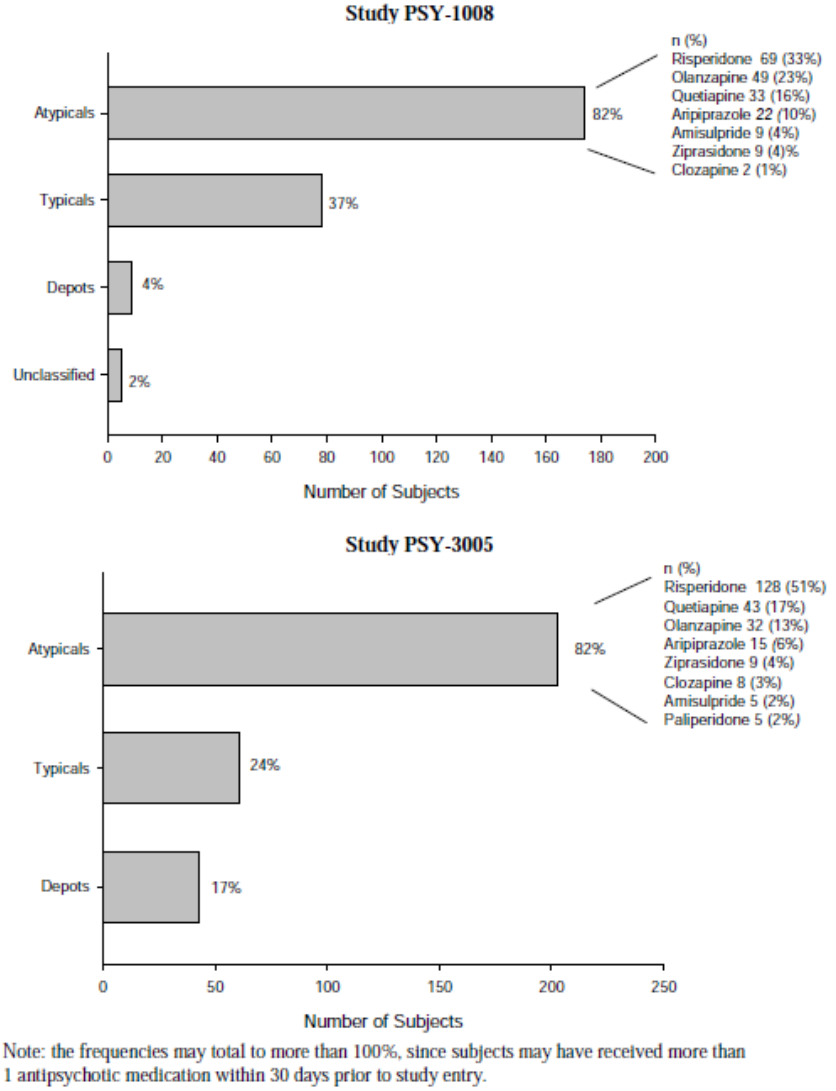
Use in maintenance treatment

The applicant provided information on long term studies (PSY-1008 and -3005) and short term studies (SCH-201, PSY-3003, PSY-3004, and PSY-3007) to support the use of paliperidone palmitate in the maintenance treatment of schizophrenia to patients currently stabilised with oral antipsychotics.

PSY-1008 was designed as an open-label, long-term, multiple-dose study to evaluate the safety, tolerability and phamacokinetics of 150 mg eq paliperidone palmitate in subjects with schizophrenia. PSY 3005 was a randomised cross over study to evaluate the overall safety and tolerability of paliperidone palmitate injected in the deltoid or gluteal muscles in subjects with schizophrenia.

In studies PSY-1008 and PSY-3005, subjects were required to be symptomatically stable prior to entry based on a PANSS total score below 60. Information regarding antipsychotic use prior to study are presented in Figure 23.

Figure 23: Antipsychotic Medications Used Prior to Study Entry in Studies PSY-1008 and PSY-3005



Note: the frequencies may total to more than 100%, since subjects may have received more than 1 antipsychotic medication within 30 days prior to study entry.

In the acute efficacy studies SCH-201, PSY-3003, PSY-3004, and PSY-3007, the majority of subjects received an atypical antipsychotic prior to study entry. The proportion of subjects who received risperidone prior to paliperidone palmitate treatment ranged from 29% to 38% across these studies;

the corresponding proportion of subjects who received other atypical antipsychotics ranged from 27% to 47% (Table 25).

Table 25

Table 1: Antipsychotics Used Prior to Study Entry in Acute Efficacy Studies SCH-201, PSY-3003, PSY-3004, and PSY-3007

	SCH-201		PSY-3003		PSY-3004		PSY-3007	
	PBO N=66 n (%)	PP N=131 n (%)	PBO N=132 n (%)	PP N=217 n (%)	PBO N=125 n (%)	PP N=389 n (%)	PBO N=160 n (%)	PP N=476 n (%)
Atypical	25 (38)	67 (51)	99 (75)	160 (74)	87 (70)	272 (70)	116 (73)	327 (69)
Oral Paliperidone	0	0	2 (2)	6 (3)	0	1 (<1)	0	0
Risperidone*	11 (17)	38 (29)	47 (36)	81 (37)	45 (36)	131 (34)	66 (41)	181 (38)
Other	15 (23)	35 (27)	67 (51)	99 (46)	56 (45)	182 (47)	68 (43)	174 (37)
Conventional	39 (59)	75 (57)	49 (37)	64 (29)	59 (47)	198 (51)	66 (41)	201 (42)
Haloperidol	23 (35)	45 (34)	28 (21)	30 (14)	36 (29)	142 (37)	44 (28)	118 (25)
Depot	1 (2)	1 (1)	3 (2)	4 (2)	0	6 (2)	9 (6)	12 (3)

* This category includes primarily oral risperidone, as well as isolated cases of RISPERDAL® CONSTA® use.
PBO = placebo; PP = paliperidone palmitate

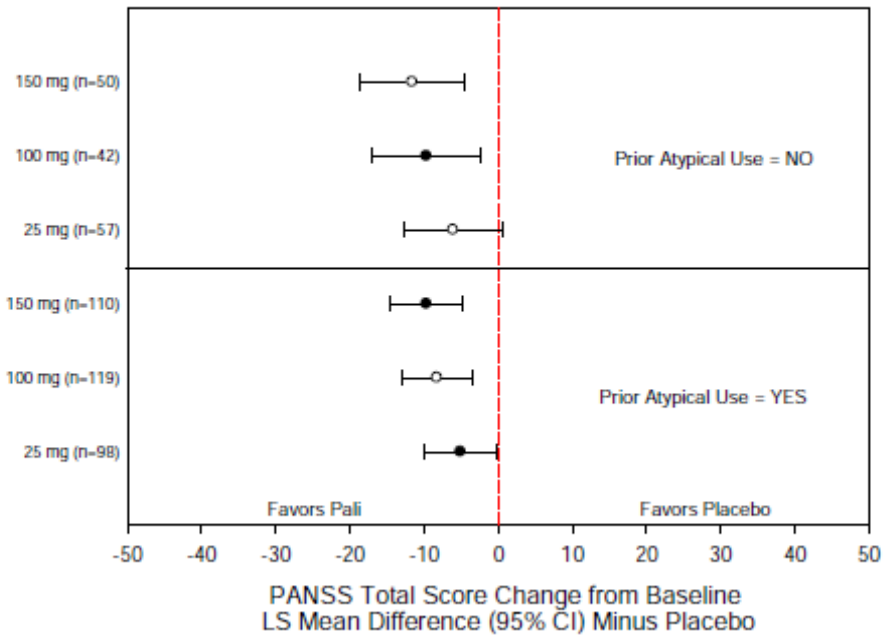
Use in initiation of treatment without prior stabilisation

The applicant provided information on short term studies (SCH-201, PSY-3003, PSY-3004, and PSY-3007) to support the use of paliperidone palmitate on initiation of treatment of schizophrenia without prior stabilisation to patients with mild to moderate psychotic symptoms and previous responsiveness to paliperidone or risperidone.

In studies SCH-201, PSY-3003, PSY-3004, and PSY-3007, subjects were required to be experiencing an acute exacerbation of schizophrenia as evidenced by a PANSS total score between 60 and 120 at entry. These subjects received a broad range of antipsychotics prior to entry, including oral and depot formulations. All subjects without prior documented exposure to risperidone or paliperidone underwent a tolerability testing (2 to 7 days), after which they were randomly assigned to receive either paliperidone palmitate or placebo. No supplementation with oral paliperidone was allowed. Since subjects were required to be experiencing an acute exacerbation at the time of entry, it was not possible to clinically stabilise them on oral paliperidone prior to randomisation.
In a post-hoc analysis of study PSY-3007 results, the mean change from baseline on the PANSS total score numerically favoured treatment with paliperidone palmitate regardless of whether subjects were previously receiving atypical antipsychotics. With the exception of the 25 mg eq group with no prior antipsychotic use, paliperidone palmitate is effective regardless of whether subjects were previously receiving atypical antipsychotics (Figure 24). Results of this post-hoc analysis performed for individual antipsychotics, including risperidone, aripiprazole, quetiapine, and olanzapine, were consistent with these findings.

Figure 24

Figure 2: Forest Plot of Least Squares Mean Change in PANSS Total Score by Prior Atypical Antipsychotic Use Prior to Study Entry (Study PSY-3007)



CI=confidence interval; LS=least-squares

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 26: Summary of Efficacy for trial SCH 201

Title: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of 2 Fixed doses (50 and 100 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia			
Study identifier	R092670-SCH-201		
Design	Run in phase included an open label dosing regimen as follows: 6 mg ER OROS paliperidone, 12 mg ER OROS paliperidone, 2 mg IR paliperidone, or 4 mg IR paliperidone, once daily for 7 days.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	64 days 7 days not applicable	
Hypothesis	Superiority		
Treatments groups	Paliperidone palmitate 50 mg eq	Day 1,8 and 36: 50 mg eq i.m 79 randomised	
	Paliperidone palmitate 100 mg eq	Day 1,8 and 36: 100 mg eq i.m 84 randomised	
	Placebo	Day 1,8 and 36: matching placebo i.m 84 randomised	
Endpoints and definitions	Primary endpoint	PANSS total score	Change in the total of the imputed Positive and Negative Syndrome Scale for Schizophrenia (PANSS) score from baseline to endpoint
	Secondary endpoint	CGI-S score	Change in the Clinical Global Impression of Severity (CGI-S) score from baseline to endpoint.
	Secondary endpoint	Responder rate	Percentage of responders defined as those who show a 30% or more reduction from baseline in the total PANSS score at the last post-randomisation assessment in the double-blind treatment period.

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat at day 64 (excluding six sites)			
Descriptive statistics and estimate variability	Treatment group	Placebo	Paliperidone palmitate 50 mg eq	Paliperidone palmitate 100 mg eq
	Number of subjects	66	63	68

	PANSS total score, mean change (standard deviation)	6.2 (18.25)	-5.2 (21.52)	-7.8 (19.40)
	CGI-S score, median change	0	0	-1
	Min, max	-2;2	-4,2	-3,2
	Number of Responders (%)	9(13.6)	21 (33.3)	25 (36.8)

Effect estimate per comparison	PANSS total score	**Comparison groups**	**Paliperidone palmitate 50 mg eq versus Placebo**
		Least square mean of difference (standard error)	-11.2 (3.41)
		90%CI	(-16.85;-5.57)
		P-value	0.001
		Comparison groups	**Paliperidone palmitate 100 mg eq versus Placebo**
		Least square mean of difference (standard error)	-14.0 (3.31)
		90%CI	(-19.51;-8.58)
		P-value	<0.0001
	CGI-score	**Comparison groups**	**Paliperidone palmitate 50 mg eq versus Placebo**
		P-value (ANCOVA on ranks)	0.004
		Comparison groups	Paliperidone palmitate 100 mg eq Placebo
		P-value (ANCOVA on ranks)	<0.001
	Responder rate	**Comparison groups**	**Paliperidone palmitate 50 mg eq versus Placebo**
		P-value (Generalized Cochran-Mantel-Haenszel test)	<0.001
		Comparison groups	**Paliperidone palmitate 100 mg eq versus Placebo**
		P-value (Generalized Cochran-Mantel-Haenszel test)	<0.001
Notes	ER OROS paliperidone: Invega, IR paliperidone: immediate release paliperidone		

Table 27: Summary of Efficacy for trial PSY-3003

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (50 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia					
Study identifier	R092670-PSY-3003				
Design	Oral tolerability testing (up to 4 days): paliperidone ER OROS 3mg/day for subjects without evidence of prior exposure to risperidone or paliperidone				
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		92 days not applicable not applicable		
Hypothesis	Superiority				
Treatments groups	Paliperidone palmitate 50 mg eq		Day 1,8 and 36 and 64: 50 mg eq i.m 94 randomised		
	Paliperidone palmitate 100 mg eq		Day 1,8 and 36 and 64: 100 mg eq i.m 97 randomised		
	Paliperidone palmitate 150 mg eq		Day 1,8 and 36 and 64: 150 mg eq i.m 30 randomised		
	Placebo		Day 1,8 and 36 and 64: matching placebo i.m 135 randomised		
Endpoints and definitions	Primary endpoint	PANSS total score	Change in the total of the imputed Positive and Negative Syndrome Scale for Schizophrenia (PANSS) score from baseline to endpoint		
	Secondary endpoint	PSP score	Change in the Personal and Social Performance Scale (PSP) from baseline to endpoint		
	Secondary endpoint	CGI-S score	Change in the Clinical Global Impression of Severity (CGI-S) score from baseline to endpoint.		
	Secondary endpoint	Responder rate	Percentage of responders defined as those who show a 30% or more reduction from baseline in the total PANSS score at the last post-randomisation assessment in the double-blind treatment period.		
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat at day 92				
Descriptive statistics and estimate variability	Treatment group	Placebo	Paliperidone palmitate 50 mg eq	Paliperidone palmitate 100 mg eq	Paliperidone palmitate 150 mg eq

	Number of subjects	132	93	94	30
	PANSS total score, mean change (standard deviation)	-4.1(21.01)	-7.9 (18.71)	-11.0 (19.06)	-5.5 (19.78)
	PSP score, mean change (standard deviation)	1.2 (16.26)	4.2 (13.21)	4.8 (15.35)	0.6 (15.52)
	CGI-S, median change	0.0	-1.0	1.0	0.0
	Min, max	(-4;3)	(-3;2)	(-3;3)	(-4;1)
	Number of Responders (%)	31(23.5)	32(34.4)	37(39.4)	7(23.3)
Effect estimate per comparison	PANSS total score	**Comparison groups**		**Paliperidone palmitate 50 mg eq versus Placebo**	
		Least square mean of difference (standard error)		-3.5 (2.67)	
		95%CI		(-8.73;1.77)	
		P-value		0.193	
		Comparison groups		**Paliperidone palmitate 100 mg eq versus Placebo**	
		Least square mean of difference (standard error)		-6.9 (2.65)	
		95%CI		(-12.12;-1.68)	
		P-value		0.019	
		Comparison groups		**Paliperidone palmitate 150 mg eq versus Placebo**	
		P-value		-	
	PSP-score	**Comparison groups**		**Paliperidone palmitate 50 mg eq versus Placebo**	
		Least square mean of difference (standard error)		5.7 (1.99)	
		95%CI		(1.80;9.64)	
		P-value		0.004	
		Comparison groups		**Paliperidone palmitate 100 mg eq versus Placebo**	

		Least square mean of difference (standard error)	6.8 (2.00)
		95%CI	(2.81;10.70)
		P-value	<0.001
		Comparison groups	**Paliperidone palmitate 150 mg eq versus Placebo**
		P-value	-
	CGI-score	**Comparison groups**	**Paliperidone palmitate 50 mg eq versus Placebo**
		P-value (ANCOVA on ranks)	0.069
		Comparison groups	**Paliperidone palmitate 100 mg eq versus Placebo**
		P-value (ANCOVA on ranks)	0.010
		Comparison groups	**Paliperidone palmitate 150 mg eq versus Placebo**
		P-value (ANCOVA on ranks)	-
	Responder rate	**Comparison groups**	**Paliperidone palmitate 50 mg eq versus Placebo**
		P-value (Generalized Cochran-Mantel-Haenszel test)	0.076
		Comparison groups	**Paliperidone palmitate 100 mg eq versus Placebo**
		P-value (Generalized Cochran-Mantel-Haenszel test)	0.012
		Comparison groups	**Paliperidone palmitate 150 mg eq versus Placebo**
		P-value (Generalized Cochran-Mantel-Haenszel test)	0.864

Table 28: Summary of Efficacy for trial PSY-3004

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq., 50 mg eq., and 100 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia			
Study identifier	R092670-PSY-3004		
Design	Oral tolerability testing (up to 4 days): paliperidone ER OROS 3mg/day for subjects without evidence of prior exposure to risperidone or paliperidone		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		92 days not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Paliperidone palmitate 25 mg eq		Day 1,8 and 36 and 64: 25 mg eq i.m 131 randomised
	Paliperidone palmitate 50 mg eq		Day 1,8 and 36 and 64: 50 mg eq i.m 129 randomised
	Paliperidone palmitate 100mg eq		Day 1,8 and 36 and 64: 100 mg eq i.m 131 randomised
	Placebo		Day 1,8 and 36 and 64: Matching placebo i.m 127 randomised
Endpoints and definitions	Primary endpoint	PANSS total score	Change in the total of the imputed Positive and Negative Syndrome Scale for Schizophrenia (PANSS) score from baseline to endpoint
	Secondary endpoint	PSP score	Change in the Personal and Social Performance Scale (PSP) from baseline to endpoint
	Secondary endpoint	CGI-S score	Change in the Clinical Global Impression of Severity (CGI-S) score from baseline to endpoint.
	Secondary endpoint	Responder rate	Percentage of responders defined as those who show a 30% or more reduction from baseline in the total PANSS score at the last post-randomisation assessment in the double-blind treatment period.
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat at day 92		

Descriptive statistics and estimate variability	Treatment group	Placebo	Paliperidone palmitate 25 mg eq	Paliperidone palmitate 50 mg eq	Paliperidone palmitate 100 mg eq
	Number of subjects	125	130	128	131
	PANSS total score, mean change (standard deviation)	-7.0 (20.07)	-13.6 (21.45)	-13.2 (20.14)	-16.1 (20.36)
	PSP score, mean change (standard deviation)	3.6 (17.07)	6.5 (15.64)	6.8 (15.37)	7.4 (14.58)
	CGI-S, median change	0.0	-1.0	-1.0	-1.0
	Min, max	(-3;2)	(-5;2)	(-3;2)	(-4;2)
	Number of Responders (%)	39(31.2)	59 (45.7)	48 (37.5)	68 (51.9)
Effect estimate per comparison	PANSS total score	**Comparison groups**		**Paliperidone palmitate 25 mg eq versus Placebo**	
		Least square mean of difference (standard error)		-6.6 (2.46)	
		95%CI		(-11.40;-1.73)	
		P-value		0.015	
		Comparison groups		**Paliperidone palmitate 50 mg eq versus Placebo**	
		Least square mean of difference (standard error)		-5.9 (2.47)	
		95%CI		(-10.76;-1.07)	
		P-value		0.017	
		Comparison groups		**Paliperidone palmitate 100 mg eq versus Placebo**	
		Least square mean of difference (standard error)		(-14.07;-4.43)	
		95%CI		-9.2 (2.45)	
		P-value		<0.001	
	PSP-score	**Comparison groups**		**Paliperidone palmitate 25 mg eq versus Placebo**	

		Least square mean of difference (standard error)	2.7 (1.92)
		95%CI	(-1.03;6.51)
		P-value (ANCOVA, Dunnett) Pvalue (ANCOVA, Bonferroni-Holm step-down)	0.262 0.154
		Comparison groups	**Paliperidone palmitate 50 mg eq versus Placebo**
		Least square mean of difference (standard error)	2.5 (1.91)
		95%CI	(-1.25;6.28)
		P-value (ANCOVA, Dunnett) Pvalue (ANCOVA, Bonferroni-Holm step-down)	0.262 0.189
		Comparison groups	**Paliperidone palmitate 100 mg eq versus Placebo**
		Least square mean of difference (standard error)	3.1 (1.92)
		95%CI	(-0.70;6.85)
		P-value (ANCOVA, Dunnett) Pvalue (ANCOVA, Bonferroni-Holm step-down)	0.257 0.110
	CGI-score	**Comparison groups**	**Paliperidone palmitate 25 mg eq versus Placebo**
		P-value (ANCOVA on ranks)	0.003
		Comparison groups	**Paliperidone palmitate50 mg eq versus Placebo**
		P-value (ANCOVA on ranks)	0.006
		Comparison groups	**Paliperidone palmitate 100 mg eq Placebo**
		P-value (ANCOVA on ranks)	0.002
	Responder rate	**Comparison groups**	**Paliperidone palmitate 25 mg eq versus Placebo**
		P-value (Generalized Cochran-Mantel-Haenszel test)	0.015
		Comparison groups	**Paliperidone palmitate 50 mg eq versus Placebo**

		P-value (Generalized Cochran-Mantel-Haenszel test)	0.271
		Comparison groups	**Paliperidone palmitate 100 mg eq versus Placebo**
		P-value (Generalized Cochran-Mantel-Haenszel test)	<0.001

Table 29: Summary of Efficacy for trial PSY-3007

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq., 100 mg eq.,and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia			
Study identifier	R092670-PSY-3007		
Design	Oral tolerability testing (4 to 6 days): paliperidone ER OROS 6mg/day for subjects without evidence of prior exposure to risperidone or paliperidone		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		92 days not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Paliperidone palmitate 25 mg eq		Day 1:Paliperidone palmitate 150 mg eq Day 8 and 36 and 64: 25 mg eq i.m 160 randomised
	Paliperidone palmitate 50 mg eq		Day 1:Paliperidone palmitate 150 mg eq Day 8 and 36 and 64: 50 mg eq i.m 165randomised
	Paliperidone palmitate 150mg eq		Day 1:Paliperidone palmitate 150 mg eq Day 8 and 36 and 64: 150 mg eq i.m 163 randomised
	Placebo		Matching placebo i.m at day 1,8, 36 and 64 164 randomised
Endpoints and definitions	Primary endpoint	PANSS total score	Change in the total of the imputed Positive and Negative Syndrome Scale for Schizophrenia (PANSS) score from baseline to endpoint
	Secondary endpoint	PSP score	Change in the Personal and Social Performance Scale (PSP) from baseline to endpoint
	Secondary endpoint	CGI-S score	Change in the Clinical Global Impression of Severity (CGI-S) score from baseline to endpoint.
	Secondary endpoint	Responder rate	Percentage of responders defined as those who show a 30% or more reduction from baseline in the total PANSS score at the last post-randomisation assessment in the double-blind treatment period.
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat at day 92		

Descriptive statistics and estimate variability	Treatment group	Placebo	Paliperidone palmitate 25 mg eq	Paliperidone palmitate 50 mg eq	Paliperidone palmitate 150 mg eq
	Number of subjects	160	155	161	160
	PANSS total score, mean change (standard deviation)	-2.9 (19.26)	-8.0 (19.90)	-11.6 (17.63)	-13.2 (18.48)
	PSP score, mean change (standard deviation)	1.7 (15.60)	2.9 (15.29)	6.1 (13.59)	8.3 (14.69)
	CGI-S, median change	0.0	-1.0	-1.0	-1.0
	Min, max	(-3;2)	(-3;2)	(-4;2)	(-4;3)
	Number of Responders (%)	32(20)	52(33.5)	66(41)	64(40)
Effect estimate per comparison	PANSS total score	**Comparison groups**		**Paliperidone palmitate 25 mg eq versus Placebo**	
		Least square mean of difference (standard error)		-5.1 (2.01)	
		95%CI		(-9.01;-1.10)	
		P-value		0.034	
		Comparison groups		**Paliperidone palmitate 50 mg eq versus Placebo**	
		Least square mean of difference (standard error)		-8.7 (2.00)	
		95%CI		(-12.62;-4.78)	
		P-value		<0.001	
		Comparison groups		**Paliperidone palmitate 150 mg eq versus Placebo**	
		Least square mean of difference (standard error)		-9.8 (2.00)	
		95%CI		(-13.71;-5.85)	
		P-value		<0.001	
		Comparison groups		**Paliperidone palmitate 100 versus Paliperidone palmitate 25 mg eq**	
		Least square mean of difference (standard error)		-3.6 (2.01)	
		95%CI		(-7.60;0.31)	
		P-value		0.071	

		Comparison groups	**Paliperidone palmitate 150 versus Paliperidone palmitate 25 mg eq**
		Least square mean of difference (standard error)	-4.7 (2.02)
		95%CI	(-8.69;-0.77)
		P-value	0.019
		Comparison groups	**Paliperidone palmitate 150 versus Paliperidone palmitate 100 mg eq**
		Least square mean of difference (standard error)	-1.1 (2.00)
		95%CI	(-5.01;2.85)
		P-value	0.588
	PSP-score	**Comparison groups**	**Paliperidone palmitate 25 mg eq versus Placebo**
		Least square mean of difference (standard error)	1.0 (1.50)
		95%CI	(-1.96;3.95)
		P-value	0.509
		Comparison groups	**Paliperidone palmitate 50 mg eq versus Placebo**
		Least square mean of difference (standard error)	4.4 (1.50)
		95%CI	(1.43;7.31)
		P-value	0.007
		Comparison groups	**Paliperidone palmitate 150 mg eq versus Placebo**
		Least square means of difference (standard error)	6.2 (1.49)
		95%CI	(3.26;9.12)
		P-value (ANCOVA, Dunnett) Pvalue (ANCOVA, Bonferroni-Holm step-down)	<0.001
	CGI-score	**Comparison groups**	**Paliperidone palmitate 25 mg eq versus Placebo**
		P-value (ANCOVA on ranks)	0.140
		Comparison groups	**Paliperidone palmitate50 mg eq versus Placebo**
		P-value (ANCOVA on ranks)	0.005

		Comparison groups	**Paliperidone palmitate 150 mg eq versus Placebo**
		P-value (ANCOVA on ranks)	<0.001
	Responder rate	**Comparison groups**	**Paliperidone palmitate 25 mg eq versus Placebo**
		P-value (Generalized Cochran-Mantel-Haenszel test)	0.007
		Comparison groups	**Paliperidone palmitate 50 mg eq versus Placebo**
		P-value (Generalized Cochran-Mantel-Haenszel test)	<0.001
		Comparison groups	**Paliperidone palmitate 150 mg eq versus Placebo**
		P-value (Generalized Cochran-Mantel-Haenszel test)	<0.001

Table 30: Summary of Efficacy for trial PSY-3006

Title: A Randomized, Double-Blind, Parallel-Group, Comparative Study of of Paliperidone Palmitate Flexible doses (50 mg eq., 100 mg eq., and 150 mg eq.) and Risperidone Long Acting Intramuscular Injection Flexible doses (25, 37.5 and 50 mg) in Subjects With Schizophrenia			
Study identifier	R092670-PSY-3006		
Design	Oral tolerability testing (4 to 6 days): paliperidone ER OROS 6mg/day for subjects without evidence of prior exposure to risperidone or paliperidone		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		92 days not applicable not applicable
Hypothesis	Non Inferiority		
Treatments groups	Paliperidone palmitate		Day1: Paliperidone palmitate 150 mg eq Day 8:Paliperidone palmitate 100 mg eq Day 36:Paliperidone palmitate 50-100 mg eq Day 64: Paliperidone palmitate 50-150 mg eq 607 randomised
	Risperdal consta		Day 8 and 22:Risperidone 25 mg Day 36: Risperidone 25-37.5 mg Day 50: same dose as day 36 Day 64: Risperidone 25-50 mg Day 78: same dose as day 64 Oral risperidone supplement: *-Day 1- week 4:* 1-6 mg/day *-Week 5-8:* If an increase in risperidone dosage is necessary, oral risperidone (1-2 mg/day) needs to be added for 3 weeks *-Week 9-12:* If an increase in risperidone dosage is necessary, oral risperidone (1-2 mg/day) needs to be added for 3 weeks 613 randomised
Endpoints and definitions	Primary endpoint	PANSS total score	Change in the total of the imputed Positive and Negative Syndrome Scale for Schizophrenia (PANSS) score from baseline to endpoint
	Secondary endpoint	PSP score	Change in the Personal and Social Performance Scale (PSP) from baseline to endpoint
	Secondary endpoint	CGI-S score	Change in the Clinical Global Impression of Severity (CGI-S) score from baseline to endpoint.
	Secondary endpoint	Responder rate	Percentage of responders defined as those who show a 30% or more reduction from baseline in the total PANSS score at the last post-randomisation assessment in the double-blind treatment period.

Results and Analysis

Analysis description	**Primary Analysis (PP)**		
Analysis population and time point description	Per Protocol at day 92		
Descriptive statistics and estimate variability	Treatment group	Paliperidone palmitate	Risperdal consta
	Number of subjects	389	376
	PANSS total score, mean change (standard deviation)	-18.6 (15.45)	-17.9(14.24)
Effect estimate per comparison	Primary endpoint	**Comparison groups**	**Risperdal Consta versus Paliperidone palmitate**
		Weighted difference (standard error)	0.4(1.02)
		95%CI	(-1.62,2.38)
Analysis population and time point description	Intention to treat at day 92		
Descriptive statistics and estimate variability	Treatment group	Paliperidone palmitate	Risperdal consta
	Number of subjects	453	460
	PANSS total score, mean change (standard deviation)	-17.1(16.37)	-16.2 (15.41)
	PSP score, mean change (standard deviation)	8.5(11.82)	8.8(11.65)
	CGI-S, mean change (standard deviation)	-0.9(0.97)	-0.9(0.93)
	Number of Responders (%)	240(53)	223(48.5)
Effect estimate per comparison	Primary endpoint	**Comparison groups**	**Risperdal Consta versus Paliperidone palmitate**
		Weighted difference (standard error)	1.2 (1.0)

		95%CI	-0.78, 3.16
	PSP-score	**Comparison groups**	**Risperdal Consta versus Paliperidone palmitate**
		Least square mean of difference (standard error)	0.2(0.74)
		95%CI	-1.22,1.69
	CGI-score	**Comparison groups**	**Risperdal Consta versus Paliperidone palmitate**
		Least square mean of difference (standard error)	0.0(0.06)
		95%CI	(-0.07,0.17)
	Responder rate	**Comparison groups**	**Risperdal Consta versus Paliperidone palmitate**
		Relative risk ratio	1.1
		95%CI	(0.97, 1.25)

Table 31: Summary of Efficacy for trial PSY-3008

Title: A Randomized, Open-Label, Parallel-Group Comparative Study of Paliperidone Palmitate Flexible doses (50, 100, or 150 mg eq.) and Risperidone Long Acting Injection Flexible doses (25, 37.5, or 50 mg) in Subjects With Schizophrenia			
Study identifier	R092670-PSY-3008		
Design	Oral tolerability testing (4 to 6 days): paliperidone ER OROS 6mg/day for subjects without evidence of prior exposure to risperidone or paliperidone		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		92 days not applicable not applicable
Hypothesis	Non Inferiority		
Treatments groups	Paliperidone palmitate		Day 1: Paliperidone palmitate 150 mg eq (deltoid only) Day 8: Paliperidone palmitate 100 mg eq (deltoid only) Day 36: Paliperidone palmitate 50 or 100 mg eq (deltoid or gluteal) Day 64: Paliperidone palmitate 50 or 100 or 150 mg eq 229 randomised
	Risperdal consta		Day 8 and 22: Risperidone 25 mg (gluteal only) Day 36: Risperidone 25-37.5 mg(gluteal only) Day 50: same dose as day 36 Day 64: Risperidone 25-50 mg Day 78: same dose as day 64 Oral risperidone supplement: *-Day 1- week 4:* 1-6 mg/day *-Week 5-8:* If an increase in risperidone dosage is necessary, oral risperidone (1-2 mg/day) needs to be added for 3 weeks *-Week 9-12:* If an increase in risperidone dosage is necessary, oral risperidone (1-2 mg/day) needs to be added for 3 weeks 223 randomised
Endpoints and definitions	Primary endpoint	PANSS total score	Change in the total of the imputed Positive and Negative Syndrome Scale for Schizophrenia (PANSS) score from baseline to endpoint
	Secondary endpoint	PSP score	Change in the Personal and Social Performance Scale (PSP) from baseline to endpoint
	Secondary endpoint	CGI-S score	Change in the Clinical Global Impression of Severity (CGI-S) score from baseline to endpoint.

	Secondary endpoint	Respon der rate	Percentage of responders defined as those who show a 30% or more reduction from baseline in the total PANSS score at the last post-randomisation assessment in the open-label treatment period.

Results and Analysis

Analysis description	**Primary Analysis (PP)**		
Analysis population and time point description	Per Protocol at day 92		
Descriptive statistics and estimate variability	Treatment group	Paliperidone palmitate	Risperdal consta
	Number of subjects	205	208
	PANSS total score, mean change (standard deviation)	-23.6(16.28)	-26.9(15.43)
	PSP score, mean change (standard deviation)	16.8(14.76)	18.6(13.92)
	CGI-S, mean change (standard deviation)	-1.5(1.24)	-1.7(1.16)
	Number of Responders (%)	145 (70.7)	163 (78.4)
Effect estimate per comparison	Primary endpoint	**Comparison groups**	**Risperdal Consta versus Paliperidone palmitate**
		Least square mean of difference (standard error)	-2.3(1.48)
		95%CI	(-5.20;0.63)
	PSP-score	**Comparison groups**	**Risperdal Consta versus Paliperidone palmitate**
		Least square mean of difference (standard error)	0.5(1.34)
		95%CI	-2.14;3.12
	CGI-score	**Comparison groups**	**Risperdal Consta versus Paliperidone palmitate**
		Least square mean of difference (standard error)	-0.1(0.11)

		95%CI	(-0.33; 0.10)
	Responder rate	**Comparison groups**	**Risperdal Consta versus Paliperidone palmitate**
		Relative risk ratio	0.9
		95%CI	(0.81;1.01)
Analysis population and time point description	Intention to treat at day 92		
Descriptive statistics and estimate variability	Treatment group	Paliperidone palmitate	Risperdal consta
	Number of subjects	228	218
	PANSS total score, mean change (standard deviation)	-20.9(18.33)	-25.6(16.51)
	PSP score, mean change (standard deviation)	14.8(16.07)	17.9(14.64)
	CGI-S, mean change	-1.4(1.32)	-1.6(1.22)
	Number of Responders (%)	147 (64.5)	164(75.2)
Effect estimate per comparison	Primary endpoint	**Comparison groups**	**Risperdal Consta versus Paliperidone palmitate**
		Least square mean of difference (standard error)	-4 (1.59)
		95%CI	-7.13;-0.89
	PSP-score	**Comparison groups**	**Risperdal Consta versus Paliperidone palmitate**
		Least square mean of difference (standard error)	1.8(1.42)
		95%CI	(-1.04;4.55)
	CGI-score	**Comparison groups**	**Risperdal Consta versus Paliperidone palmitate**
		Least square mean of difference (standard error)	- 0.2(0.11)
		95%CI	(-0.44; 0.01)
	Responder rate	**Comparison groups**	**Risperdal Consta versus Paliperidone palmitate**
		Relative risk ratio	0.9
		95%CI	(0.76;0.97)

Table 32: Summary of Efficacy for trial PSY-3001

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Evaluating Paliperidone Palmitate in the Prevention of Recurrence in Subjects With Schizophrenia		
Study identifier	R092670-PSY-3001	
Design	Oral tolerability testing (up to 4 days): paliperidone ER OROS 3mg/day for subjects without evidence of prior exposure to risperidone or paliperidone Open label transition phase (9 weeks): Paliperidone palmitate 50 mg eq at day 1 and 8 Paliperidone palmitate flexible dosing from week 5 (25, 50, or 100 mg eq) Open label maintenance phase (24 weeks): Paliperidone palmitate 12 weeks of flexible dosing followed by 12 weeks of fixed dosing based on the dose established during the first half of maintenance phase. Double blind recurrence prevention phase (variable): see Treatments groups. Extension Phase (52 weeks): Oral supplementation (3-12 mg/day) was allowed during Week1-8 Paliperidone palmitate 50 mg eq at day 1 (not administered until 4 weeks after the last double blind phase injection) Paliperidone palmitate flexible dosing from week 2 (25, 50, 75 or 100 mg eq)	
	Duration of main phase: Duration of transition/maintenance phase: Duration of Extension phase:	variable 33 weeks 52 weeks
Hypothesis	Superiority	
Treatments groups	Paliperidone palmitate	Paliperidone palmitate fixed dose every 4 weeks (equivalent to the final dose used in the maintenance phase) 206 randomised
	Placebo	Matching placebo every 4 weeks (equivalent to the final dose used in the maintenance phase) 204 randomised

Endpoints and definitions	Primary endpoint	Time to recurrence	Time between subject randomization to treatment and the first documentation of a recurrence event during the double-blind recurrence prevention phase. Subjects who meet at least 1 of the criteria for recurrence while on double-blind treatment at the time of study completion for the primary analysis are considered to have had a recurrence event. All other subjects without a recurrence at the end of study for the primary analysis will be considered censored at the end of study. Relapse is defined as one of the following : - Psychiatric hospitalization (involuntary or voluntary admission to a psychiatric hospital for decompensation of the subject's schizophrenic symptoms), or - For PANSS: increase of 25% in the total PANSS score from randomization for 2 consecutive assessments separated by 3 to 7 days if the score at randomization was >40, or a 10-point increase in the total PANSS score from randomization for 2 consecutive assessments separated by 3 to 7 days if the score at randomization was ≤40, or - Deliberate self-injury and/or violent behaviour resulting in suicide or in clinically significant injury to the subject or another person or property damage, or - Suicidal or homicidal ideation and aggressive behaviour that was clinically significant (in frequency and severity) in the investigator's judgment, or - For PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behaviour), P6 (suspiciousness/persecution), P7 (hostility) or G8 (uncooperativeness): a score ≥5 after randomization for 2 consecutive assessments separated by 3 to 7 days on any of the above PANSS items if the maximum score for the above PANSS items was ≤ 3 at randomization, or a score ≥6 after randomization for 2 consecutive assessments separated by 3 to 7 days on any of the above PANSS items if the maximum score for the above PANSS items was 4 at randomization.
	Secondary endpoint	PANSS total score	Change in the total of the imputed Positive and Negative Syndrome Scale for Schizophrenia (PANSS) score from baseline to endpoint

	Secondary endpoint	PSP score	Change in the Personal and Social Performance Scale (PSP) from baseline to endpoint
	Secondary endpoint	CGI-S score	Change in the Clinical Global Impression of Severity (CGI-S) score from baseline to endpoint.
	Secondary endpoint	Responder rate	Percentage of responders defined as those who show a 30% or more reduction from baseline in the total PANSS score at the last post-randomisation assessment in the double-blind treatment period.

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intention to Treat (Interim analysis)		
Descriptive statistics and estimate variability	Treatment group	Paliperidone palmitate	placebo
	Number of subjects	156	156
	Number (%) of Subjects Experiencing Recurrence and Time to Recurrence	15(9.6)	53 (34.0)
Effect estimate per comparison	Time to recurrence	**Comparison groups**	**Paliperidone palmitate versus Placebo**
		Chisquare	29.411
		P-value (Log rank test)	<0.0001
Analysis population and time point description	Intention to treat (All subjects through the time of study termination)		
Descriptive statistics and estimate variability	Treatment group	Paliperidone palmitate	Placebo
	Number of subjects	205	203
	Number (%) of Subjects Experiencing Recurrence and Time to Recurrence	36 (17.6)	97 (47.8)

	PANSS total score, mean change (standard deviation)	2.5 (12.16)	11.1 (16.60)
	PSP score, mean change (standard deviation)	-1.5 (11.53)	-7.2 (13.03)
	CGI-S, median change	0.0	0.0
	Min, max	(-1;3)	(-1;4)
Effect estimate per comparison	Time to recurrence	**Comparison groups**	**Paliperidone palmitate versus Placebo**
		Chisquare	48.362
		P-value (Log rank test)	<0.0001
	PANSS total score	**Comparison groups**	**Paliperidone palmitate versus Placebo**
		Least square mean of difference (standard error)	-8.6 (1.45)
		95%CI	(-11.41;-5.70)
		P-value	<0.0001
	PSP-score	**Comparison groups**	**Paliperidone palmitate versus Placebo**
		Least square mean of difference (standard error)	5.3 (1.19)
		95%CI	(2.99;7.67)
		P-value	<0.0001
	CGI-score	**Comparison groups**	**Paliperidone palmitate versus Placebo**
		P-value (ANCOVA on ranks)	<0.0001

Table 33: Summary of Efficacy for trial PSY-3002

Title: A Randomized, Double Blind, Parallel-Group Comparative Study of Flexibly Dosed Paliperidone Palmitate (25, 50, 75, or 100 mg eq.) Administered Every 4 Weeks and Flexibly Dosed RISPERDAL® CONSTA® (25, 37.5, or 50 mg) Administered Every 2 Weeks in Subjects With Schizophrenia			
Study identifier	R092670-PSY-3002		
Design	Oral tolerability testing (up to 4 days): paliperidone ER OROS 3mg/day for subjects without evidence of prior exposure to risperidone or paliperidone		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		372 days 7 days not applicable
Hypothesis	Non Inferiority		
Treatments groups	Paliperidone palmitate		Baseline (Day 1) : 50 mg eq i.m. Week 1 (Day 8): 50 mg eq i.m. Week 3: Placebo i.m. Weeks 5 to 51: Flexible dosing with 25, 50, 75, or 100 mg eq i.m. During the first 4 weeks of the double-blind treatment period, oral placebo tablets will be taken once daily. 379 randomised
	Risperdal consta		Baseline (Day 1): Placebo i.m. risperdal consta 25 mg i.m. Week 1: risperdal consta 25 mg i.m Week 3: risperdal consta 25 mg i.m Weeks 5 to 51: risperdal consta 25, 37.5, or 50 mg i.m Oral risperidone supplement During the first 4 weeks of the double-blind treatment period, oral risperidone 1 to 6 mg/d will be taken once daily. 370 randomised
Endpoints and definitions	Primary endpoint	PANSS total score	Change in the total of the imputed Positive and Negative Syndrome Scale for Schizophrenia (PANSS) score from baseline to endpoint
	Secondary endpoint	PSP score	Change in the Personal and Social Performance Scale (PSP) from baseline to endpoint
	Secondary endpoint	CGI-S score	Change in the Clinical Global Impression of Severity (CGI-S) score from baseline to endpoint.
	Secondary endpoint	Responder rate	Percentage of responders defined as those who show a 30% or more reduction from baseline in the total PANSS score at the last post-randomisation assessment in the double-blind treatment period.
Results and Analysis			

Analysis description	**Primary Analysis (PP)**		
Analysis population and time point description	Per Protocol at day 372		
Descriptive statistics and estimate variability	Treatment group	Paliperidone palmitate	Risperdal consta
	Number of subjects	288	282
	PANSS total score, mean change (standard deviation)	-11.6 (21.22)	14.4 (19.76)
Effect estimate per comparison	PANSS total score	Comparison groups	Paliperidone palmitate Risperdal Consta
		Least square mean of difference (standard error)	-2.6 (1.64)
		95%CI	(-5.84;0.61)
Analysis population and time point description	Intention to treat at day 372		
Descriptive statistics and estimate variability	Treatment group	Paliperidone palmitate	Risperdal consta
	Number of subjects	343	331
	PANSS total score, mean change (standard deviation)	-9.5 (21.95)	-13.0 (20.63)
	PSP score, mean change (standard deviation)	3.7 (16.39)	5.2 (15.13)
	CGI-S, mean change	-0.4 (1.25)	-0.6 (1.24)
	Number of Responders (%)	152(44.3)	179(54.4)
Effect estimate per comparison	Primary endpoint	**Comparison groups**	**Risperdal Consta Versus Paliperidone palmitate**
		Least square mean of difference (standard error)	-3.8 (1.59)
		95%CI	(-6.96;-0.74)
	PSP-score	Comparison groups	Paliperidone palmitate Risperdal Consta

		Least square mean of difference (standard error)	1.7 (1.17)
		95%CI	(-0.61;3.97)
	CGI-score	**Comparison groups**	**Risperdal Consta Versus Paliperidone palmitate**
		Least square mean of difference (standard error)	-0.2 (0.09)
		95%CI	(-0.41;-0.06)
		P-value	
	Responder rate	**Comparison groups**	**Risperdal Consta Versus Paliperidone palmitate**
		Relative risk ratio	0.8
		95%CI	(0.70; 0.95)

2.5.3. Discussion on clinical efficacy

Short term studies

In placebo controlled studies (SCH-201, PSY-3003, 3004 and 3007), the treatment groups were well balanced with respect to diagnosis (80 to 90% of paranoid subtype across studies), severity (about 50% with at least marked severity), and prior hospitalisation for psychosis (about 60% with 3 or more prior hospitalisations). Overall, these studies have demonstrated short term efficacy for paliperidone palmitate in patients with schizophrenia.

In study SCH-201, statistically significant and clinically relevant effects were shown for the primary and secondary endpoints (changes from baseline in PANSS total score, CGI-S and responder rate) at both 50 and 100 mg doses versus placebo.

In study PSY-3003, results were less compelling. In this study, statistically significant result for the primary efficacy endpoint was obtained for the 100 mg dose only (p=0.019). A minimal effect on the PANSS total score was observed for the 150 mg dose (-5.5) together with high withdrawal rate due to lack of efficacy (43%). Furthermore, statistically significant treatment-by-country and treatment-by-baseline PANSS score interactions (p<0.10) were observed in the primary efficacy model (Figure 5). In the CHMP's view, the treatment-by-country interaction seemed to be due to lack of effect in US patients. A trend towards a treatment-by-baseline BMI interaction was also observed.

Results from PSY-3004 also suggested a treatment-by-country interaction that was potentially confounded by a treatment-by-baseline BMI interaction (Figure 6). In this study, all tested doses demonstrated statistical significance for the changes from baseline in PANSS scores and CGI-S. However, changes from baseline in PSP score failed to demonstrate statistical significant difference (p=0.154 for 25 mg; p=0.189 for 50 mg and p=0.110 for 100 mg). In addition, difference in the percentage of responder rate was not statistically significant for the 50 mg dose (p=0.271).

In study PSY-3007, a new dosing regimen was introduced in order to increase the initial exposure to paliperidone palmitate in overweight/obese patients using a weight adjusted needle length. As a result, no significant treatment-by country interaction was observed although the differences versus placebo were less pronounced in US patients for the primary endpoint (-2.5, -3.6, and -6.6 for the 25, 100, and 150 mg groups, respectively). Similarly to studies PSY-3003 and 3004, the distribution of baseline

BMI differed across countries and effect in obese US patients was not demonstrated (Figure 7). In normal weight patients, treatment effect was significant in all dose groups (25, 100 and 150 mg) increasing with dose. In overweight patients, there were only significant treatment effects in the 100 and 150 mg dose groups, increasing with dose, whereas in obese patients there were no significant treatment effects. Nonetheless, in this study, significant effects were demonstrated over placebo for all doses on the PANSS total score analysis ($p=0.034$ for 25 mg eq, $p<0.001$ for both 50 and 100 mg eq), supported by results for secondary endpoints (changes from baseline in CGI-S, PSP and responder rates) for the two higher doses (100 mg and 150 mg). In addition, a clear dose response was observed.

In the two non-inferiority studies (PSY-3006 and -3008), there were no major imbalances between treatment groups. Overall, PSY-3006, a double blind study, has demonstrated non inferiority of paliperidone palmitate versus Risperdal consta for the short term efficacy in patients with schizophrenia whereas PSY-3008, an open-label study has failed to demonstrate this non inferiority. In study PSY-3006 using initial doses of 150 mg eq at day 1 and 100 mg eq at day 8 (final recommended enhance dosing regimen), non inferiority was demonstrated for the primary endpoint in the PP and ITT analyses: 0.4 [-1.62-2.38] and 1.2 [-0.78-3.16], respectively. This was supported by the secondary analyses of responder rates, change in PSP and CGI-S scores (Figures 9, 10 and 11).

Furthermore, there was no treatment-by-country interaction and there were no differences between the treatments in all countries with a substantial number of subjects enrolled (including US). However, the non-inferiority could not formally be concluded for obese patients (Figure 12), with lower 97.5% confidence limit of -3.13, -0.76, and -6.93, respectively as opposed to patients with normal weight and overweight patients, suggesting that paliperidone palmitate could be less effective in obese patients at the tested doses. The tendency for a lower efficacy of paliperidone palmitate in obese patients was also observed in the failed study PSY-3008 (Figure 14) as opposed to Risperdal consta.

In light of the above, the CHMP requested the applicant to further discuss the results in short term efficacy for obese patients. Both pharmacokinetic data and efficacy data indicated a lower exposure to paliperidone and poorer efficacy outcomes in this population suggesting an inadequacy of the proposed dosing regimen tested in PSY-3007.

The applicant provided the following argumentation:

- Pharmacokinetic results from earlier studies with gluteal injections conducted with the older dosing regimen showed a difference in initial plasma exposure in the obese and overweight subgroup as compared to subjects in the normal BMI subgroup. This difference was more pronounced in the early part of treatment (i.e., prior to the third injection) and was less relevant at steady-state. The results of a population PK analysis confirmed that subjects with a higher body weight/BMI have a decreased F2 parameter, which is the fraction of dose reaching the systemic circulation relatively quickly. This results in lower concentrations early after injection, and a slower attainment of steady state.

- The effect of BMI on PK is most pronounced at initiation of treatment and diminishes over time once steady state is achieved. Population PK analysis also suggested that deltoid dosing and drug administration with a longer needle in the deltoid muscle is associated with a higher F2 parameter. Therefore, results of population PK simulations indicated that initiating dosing with paliperidone palmitate at a dose of 150 mg eq. into the deltoid muscle (with a longer needle for heavier individuals) would be sufficient to alleviate the influence of BMI on the initial plasma concentrations of paliperidone. This expectation has been realised in recently conducted Phase 3 studies utilizing the recommended dosing regimen (PSY-3007 and PSY-

3006). The differences in paliperidone plasma concentration during the early part of treatment (prior to the third dose) between the different BMI subgroups were found to be negligible.

- Pharmacokinetic results from the open-label phase I safety long-term study PSY-1008 suggested a small difference in median plasma concentration for subjects in the obese BMI category as compared to normal-BMI subjects. However, when PANSS total score changes from baseline were compared in these 3 subgroups, no statistical difference was found.
- Earlier Phase 3 studies conducted with paliperidone palmitate showed a notable difference in treatment effect between normal and overweight/obese subjects. This difference was reduced in the more recent set of studies conducted with the revised dosing regimen. Although the magnitude of effect was numerically smaller in obese and overweight subjects as compared to normal-weight subjects, the effect was still statistically significantly in favour of paliperidone palmitate across all 3 BMI categories.
- In the long-term relapse prevention Study PSY-3001, a significant treatment effect in favour of paliperidone palmitate was observed in all 3 BMI subgroups, suggesting that once a therapeutic response is achieved, the influence of BMI is negligible.

On the basis of the applicant's response, the CHMP considered that the current proposed dosing regimen within adjustments within the range of 25 to 150 mg eq. was acceptable, provided that a statement in the SPC is included to reflect that overweight or obese patients may require doses in the higher dose range.

Long term studies

The relapse prevention study (PSY-3001) was stopped at a pre-planned interim analysis when 68 patients had experienced a relapse, 34.0% in the placebo group and 9.6% in the paliperidone palmitate group showing superiority over placebo ($p<0.0001$).

This was confirmed by the final analysis (including relapses between the interim analysis and study termination, Figure 16). For all causes for relapse, there were more relapses on placebo treatment (Table 20). In addition, the primary time to relapse analysis was supported by highly significant results in favour of paliperidone palmitate in the analysis of the secondary efficacy endpoints: change in PANSS total score, CGI-S and PSP scores. Relapse prevention was similar in the two dominating regions US and Eastern Europe. Neither was there any difference in effect depending on baseline BMI. Statistical significance was reported for normal, overweight as well obese patients.

In study PSY-3002, non-inferiority could not be concluded, the lower confidence limit was below the pre-specified non-inferiority margin of 5 points in both PP and ITT analyses (Table 22 and Figure 17). The tendency towards a better effect of Risperdal consta was supported by the results for the secondary endpoints, particularly a significant difference in responder rates (44.3% versus 54.4%). There was no treatment-by-region interaction ($p=0.580$) and the observed regional differences might be due to random fluctuations. Despite the primary analysis was inconclusive, results in patients from Western Europe could be considered valuable for the extrapolation of the overall results to the intended EU population (Figure 18). The treatment-by-baseline BMI interaction approached statistical significance at the pre-specified 10% significance level ($p=0.108$) suggesting a suboptimal effect of paliperidone palmitate in obese patients (Figure 19). In addition, no relevant differences between paliperidone palmitate and risperidone consta were observed for non obese patients.

Dose response

In pooled analyses performed across all placebo-controlled short-term studies (Figure 20), significant effects versus placebo were demonstrated for the dose range 25-150 mg with an increased effect above 50 mg suggesting that the recommended maintenance dose range 25-150 was appropriate.

Use of depot formulation

The indication initially applied for was: treatment of adult patients with schizophrenia.

According to the Appendix to Note for Guidance on the clinical investigation of medicinal products in the treatment of schizophrenia – Methodology of clinical trials concerning the development of depot preparations of approved medicinal products in schizophrenia (CPMP/EWP/49/01, 2003), "Depot preparations are meant for maintenance treatment, once a patient is stabilised satisfactorily on an oral preparation. Therefore a patient usually will continue on the product that has been shown to be effective for him. It would be very rare to start a patient on a depot preparation, as e.g. dose titration is not possible, an acute effect may be needed or undesirable effects may occur, in which case the preparation cannot be withdrawn". The CHMP therefore requested the applicant to further discuss the proposed indication which included the possibility to start treatment without prior stabilisation on oral treatment. Importantly, in the absence of a direct comparative biovailability study of paliperidone palmitate versus oral paliperidone (Invega), the switching from oral treatment without a need to supplement with oral dosing and the onset of efficacy of paliperidone palmitate versus oral paliperidone should be addressed. Therefore, the CHMP agreed to convene the Central Nervous System Scientific Advisory Group (CNS SAG) to discuss the clinical role of long-acting injectable antipsychotic treatment used in schizophrenia.

The CNS SAG was held on 13 July 2010 and the main conclusions were the following:

- Long-acting injectable antipsychotic treatment without prior stabilisation on oral treatment should not be used in treatment-naive patients or in acutely disturbed schizophrenia patients;
- Long-acting injectable antipsychotic treatment without prior stabilisation on oral treatment could, however, depending on the physician's judgement, be considered in a restricted group of patients with an established diagnosis, consisting of patients with mild to moderate relapses of disease, patients with compliance difficulties, and patients who have a preference for treatment with injectable depot formulations.
- The timeframe for onset of action would depend on the clinical situation as described above;
- Initial coverage (e.g. for the first week of treatment), might be an acceptable approach, however, no clinical data have been presented on simultaneous administration of oral and intramuscular paliperidone palmitate;
- The possibility of tight dose titration when initiating therapy relate to the acuteness of the clinical situation. It is clear that injectable depot formulations do not provide the same flexibility for dose titration as oral formulations or short-acting injectable formulations;
- It is not considered acceptable to administer a depot preparation to patients without prior experience regarding tolerability of the active substance. The dosage and the interval of the initial exposure to the oral preparation prior to initiation of a depot preparation is a crucial factor that has to be specified.
- The design, including study population, of the studies in the paliperidone palmitate is considered appropriate for use in a restricted population as discussed above. In general, clinical trials need to address different treatment settings and patient populations with different compliance.

To support the indication initially applied for, the applicant's argumentation related to pharmacokinetics and efficacy aspects can be summarised as follows:

- In contrast to older oil-based depot antipsychotics, which were more appropriate for maintenance treatment due to the delayed attainment of therapeutic plasma drug concentrations, paliperidone palmitate was formulated as an aqueous suspension, allowing for immediate and sustainable release of paliperidone and providing therapeutic plasma drug concentrations as rapidly as the oral paliperidone formulation. Thus, the clinical rationale for stabilising patients on oral therapy prior to switching to the injectable antipsychotic was anticipated not to apply to paliperidone palmitate;
- Clinical data for paliperidone palmitate based on the enhanced dosing regimen (including a loading dose of 150 mg eq. in the deltoid muscle on Day 1) showed statistically significant improvement over placebo with regard to PANSS total score that occurred as early as Day 8 and is maintained at subsequent time points.
- There was no statistical difference between paliperidone palmitate and Risperdal consta treatment groups in study PSY-3006 with regard to change from baseline in PANSS total score during the first 36 days of treatment. Given that the data from the Risperdal consta group during this period effectively reflects treatment with oral risperidone due to the delay in the release of risperidone from its LAI formulation, this indicates that paliperidone palmitate achieves and maintains a treatment effect similar to that of oral risperidone.
- Thus, time to onset of efficacy achieved with paliperidone palmitate is comparable to that achieved with oral paliperidone PR, as well as other marketed oral antipsychotics, including risperidone, and appears to be within clinically acceptable limits in the management of acute schizophrenia without requiring oral stabilisation.
- A bioavailability study directly comparing orally administered paliperidone PR and paliperidone palmitate using a cross-over design was not conducted due to the availability of comparative PK data from Study SCH-201 and the difficulties related to conducting a crossover study (long wash-out required). It was not the intent to bridge to efficacy from the oral formulation, and hence a full Phase 3 development programme was conducted. Instead, the relative bioavailability of oral paliperidone and paliperidone palmitate was evaluated at steady state in SCH-201 and by means of a meta-analysis, supported by population modeling. The results consistently confirmed that paliperidone palmitate 25, 75, and 150 mg eq. provide sustained steady-state paliperidone plasma concentrations within the simulated exposure window for 2, 6, and 12 mg doses of paliperidone PR, respectively.
- Because injection site and administered dose significantly affect the initial release, the initial exposure (Day 1-8) observed in SCH-201 did not reflect the initial exposure following the recommended dosing regimen and, therefore, did not allow to draw any conclusions with respect to need for oral coverage. Alternatively, a meta analysis was conducted, which showed that within 24 to 48 hours upon injection of the first deltoid loading dose of paliperidone palmitate (150 mg eq.), plasma paliperidone concentrations are comparable to those obtained upon initiation of the recommended dose of paliperidone PR (6 mg).

On the basis of the SAG recommendations and applicant's responses, the CHMP considered the following:

- The onset of efficacy for oral paliperidone was by day 4 and for paliperidone palmitate some days later by day 8. Statistical significant effects compared to placebo have been shown from

day 8 onwards for paliperidone palmitate, which is considered comparable to other available antipsychotics;

- The oral supplementation is not required for paliperidone palmitate. There was no statistical difference between paliperidone palmitate and Risperdal consta (requiring oral supplementation for the first 3 weeks) treatment groups in study PSY-3006 with regard to change from baseline in PANSS total score during the first 36 days of treatment. In addition a numerically higher proportion of responders for paliperidone palmitate was observed at every time point from day 4 as compared to Risperdal consta.
- The treatment without prior oral stabilisation should be restricted to selected patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed.

Therefore, the CHMP initially recommended the following indication:

"Xeplion is indicated for maintenance treatment of schizophrenia in patients stabilised with oral paliperidone or risperidone.

In selected patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, Xeplion may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed."

During an oral explanation held on 13 December 2010, the applicant argued that the maintenance treatment should also be indicated for the patients stabilised on other antipsychotics if prior responsiveness to paliperidone or risperidone has been established. The applicant's view can be summarised as follows:

- The majority of the clinical program (9 out of 10 studies) did not require oral stabilisation prior to entry in short or long term studies;
- Results from studies PSY-1008 and PSY-3005 (allowed stable patients to enter) were supportive of efficacy following stabilisation on a diversity of antipsychotics including conventional and atypical agents other than risperidone or paliperidone (43%);
- In pooled short term studies (SCH-201, PSY-3003, -3004 and -3007), treatment effects favored paliperidone regardless of prior antipsychotic use;
- In pooled double blind studies, the incidence of EPS related events such as akhatisia and parkinsonism was comparable in patients with and without prior exposure to risperidone or paliperidone ;
- Switching from various oral antipsychotics to depots is generally effective and well tolerated[7]

Having considered the oral explanation provided by the applicant, the CHMP considered that there is a lack of evidence to support the proposed initial dose of paliperidone palmitate (150 mg at day 1 and 100 mg at day 8) to ensure safe and effective use for paliperidone palmitate in patients stabilised on other antipsychotics than risperidone and paliperidone.

Considering the above and possible switch from risperidone long acting injectable to paliperidone palmitate, the CHMP recommended the following final indication:

[7] Moller HJ et al, Int Clin Psychopharmacol. 20(3):121-30,2005.

"XEPLION is indicated for maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone.

In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, XEPLION may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed."

The applicant agreed with the above final wording for the indication. The applicant has also proposed to perform a drug utilisation study to assess the usage of paliperidone palmitate in the approved indication (schizophrenia) in Europe. A protocol outline has been provided as part of the risk management plan and final protocol is intended to be submitted as part of a follow up measure.

During the evaluation, the proposed legal status "medicinal product subject to medical prescription" was also discussed by the CHMP, in view of the pharmaceutical characteristics of the depot formulation and potential consideration to reserve the treatments for hospital environment. The CHMP concluded that the proposed legal status for paliperidone palmitate was adequate considering its pharmaceutical properties and safety profile including the lack of evidence of risk of post injection delirium and somnolence syndrome which would require follow up in hospital setting.

2.5.4. Conclusions on the clinical efficacy

The CHMP concluded that efficacy in reducing symptoms of schizophrenia (using the standard PANSS total score) and preventing occurrence of new symptoms was demonstrated in the proposed dosing regimen for Xeplion (paliperidone).

2.6. Clinical safety

The safety database presented in the dossier included the following datasets: population Phase 2/3 short term trials **(SCH-201, PSY-3003, -3004, -3007**), long term trials (**PSY-3001, PSY-3005)**, non inferiority short and long term trials (**PSY-3006, -3008 and -3002),** clinical pharmacology trials in patients with schizophrenia.

In addition to these datasets, study PSY-1008 was an open-label, long-term, multiple-dose to primarily evaluate the pharmacokinetic of 150 mg eq. paliperidone palmitate and the safety and tolerability of flexible doses of paliperidone palmitate in the treatment of subjects with schizophrenia and safety results of this phase I study are also presented. The study consisted of 2 phases, a screening and washout phase of up to 21 days and a 53-week open-label treatment phase including an end-of-study or early withdrawal visit. There were 2 treatment groups in this study, treatment A and treatment B. Treatment A represented subjects who received paliperidone palmitate 150 mg eq. throughout the study and who participated in intensive PK sampling. Treatment B represented subjects who were unable to tolerate the 150 mg eq. dose or who were unwilling to continue with intensive PK sampling. Subjects in treatment group B received flexible doses of paliperidone palmitate in the range of 50 to 150 mg eq. All subjects were initially assigned to treatment A and received the first dose of paliperidone palmitate 150 mg eq. in the deltoid muscle. One week later, subjects in treatment group A received a second injection in the deltoid muscle while subjects in treatment group B received the second injection in either the deltoid or gluteal muscle. The 12 subsequent i.m. injections were administered every 4 weeks in either the deltoid or gluteal muscle (Treatment A and Treatment B).

Patient exposure

A total of 3605 subjects with schizophrenia received at least one dose of paliperidone palmitate in the 9 completed phase 2/3 studies, 713 received placebo, and 1199 received Risperdal consta. The combined exposure to paliperidone palmitate in all completed Phase 2/3 studies was 1559.8 patient-years. Of the 3605 subjects treated with paliperidone palmitate, 203 subjects received treatment with paliperidone palmitate during the open-label transition/maintenance phases of study PSY-3001 and subsequently were randomly assigned to placebo in the double-blind phase of this study. Of the 713 placebo-treated subjects, 510 subjects received placebo throughout the entire study in the short term trials PSY-3003, PSY-3004, PSY-3007, and SCH-201.

In study PSY-1008, 212 subjects received at least one dose of paliperidone palmitate 150 mg eq. Combined cumulative exposure to paliperidone palmitate in the 9 Phase 2/3 studies and the long-term safety study PSY-1008 was 1704.8 patient-years, based on 3817 subjects who received at least 1 dose.

Adverse events

In pooled studies PSY-3003 and -3004, treatment-emergent adverse events occurred at similar rates for paliperidone palmitate 25 to 100 mg eq. (70% to 75%) and placebo (74%) groups. Treatment-emergent adverse events occurred at higher rates in subjects receiving paliperidone palmitate 150 mg eq. (83%), although the number of subjects in this treatment group (n=30) was small. Many of the common treatment-emergent adverse events (adverse events in the Nervous System and Psychiatric Disorders System Organ Classes, especially schizophrenia and psychotic disorder), were reported at a higher incidence in placebo-treated subjects.

In study PSY-3007, the frequency of treatment-emergent adverse events in this study was slightly lower than for the pooled PSY-3003, -3004 studies for paliperidone palmitate 50 to 150 mg eq. (60% to 63%) and placebo (65%), and was consistent with results of study SCH-201. The safety profile of the 150 mg eq. dose in study PSY-3007 was similar to that of the lower doses.

In study PSY-1008, 87% (184/212) experienced treatment-emergent adverse events during the long-term open-label study period. Most adverse events were mild or moderate in severity. The most frequently reported treatment-emergent adverse events (>10%), in subjects receiving only paliperidone palmitate 150 mg eq. for at least 1 year were nasopharyngitis (19.2%), tachycardia (19.2%), injection site pain (14.4%), headache (12.5%), insomnia (11.5%), and weight increased (10.6%) (see table S5).The most frequently reported adverse events in subjects who required dose adjustment included dystonia, asthenia, sluggishness, and orthostatic hypotension.

In study PSY-3001, reporting rates for the transition/maintenance (67%) and double-blind phases (44%) suggested that subjects who continue to receive paliperidone palmitate following a period of stabilization may have a lower incidence of newly occurring adverse events after stabilization compared to subjects for who treatment is newly initiated. Overall, adverse events were reported at similar rates for paliperidone palmitate and placebo (44% versus. 45%) during the double-blind phase. For most of the common adverse events, reporting rates were similar between the 2 treatment groups. A notable exception was weight increased, which was more common in the paliperidone palmitate group than the placebo group (7% versus. 1%). There was no evidence of a withdrawal syndrome or rebound phenomenon in subjects who abruptly discontinued paliperidone palmitate treatment (ie, switched to placebo). In the open-label extension phase, the pattern of newly occurring adverse events, as well as serious adverse events, was consistent with that in the double-blind phase. During this phase, adverse events were reported for 56% of subjects. The most common adverse event terms were consistent with those reported during the earlier phases of the study.

In study PSY-3005, the incidence and severity of treatment-emergent adverse events was similar across dose groups and injection site-sequence groups for gluteal and deltoid injections. Reporting rates for common adverse events were similar to those for 25 to 100 mg eq. doses of paliperidone palmitate in the pooled PSY-3003/PSY-3004 studies. As observed for study PSY-3001, reporting rates for many common adverse events tended to be lower through long-term treatment.

In study PSY-3006, adverse events occurred at similar rates in the paliperidone palmitate and Risperdal consta groups (58% versus. 53%). The most common adverse events (occurring in ≥5% of the subjects) were insomnia, headache, somnolence, and injection site pain for the paliperidone palmitate group and insomnia and headache for the Risperdal consta group.

In study PSY-3008, the incidence of treatment-emergent adverse events in the open-label was generally comparable to that in other studies and was similar between paliperidone palmitate and Risperdal groups (73% versus. 75%).

In study PSY-3002, the overall reporting rates for adverse events were similar for subjects receiving paliperidone palmitate and Risperdal consta (76% versus 79%). The most common adverse events in study PSY-3002 were psychiatric disorders, for which the incidence was similar between treatment groups (50% versus. 52%); however, a larger proportion of subjects in the paliperidone palmitate group (18% versus. 14% for Risperdal consta) had a severe psychiatric adverse event (mainly psychotic disorder and schizophrenia).

Adverse Drug Reactions reported by at least 2% of paliperidone palmitate-treated Subjects in the key studies are presented in Table 34.

Table 34. Adverse Drug Reactions Reported by at Least 2% of Paliperidone Palmitate-Treated Subjects in Key Studies (Studies R092670-SCH-201, PSY-3001, PSY-3002, PSY-3003, PSY-3004, PSY-3005, PSY-3006, PSY-3007, PSY-3008, and PSY-1008)

Body System or Organ Class	Dictionary-derived Term	Frequency Category[a]
Cardiac disorders	Tachycardia	Common
Gastrointestinal disorders	Constipation	Common
	Diarrhoea	Common
	Nausea	Common
	Vomiting	Common
General disorders and administration site conditions	Injection site reactions	Common
Infections and infestations	Upper respiratory tract infection	Common
Investigations	Weight increased	Common
Nervous system disorders	Akathisia	Common
	Dizziness	Common
	Headache	Very common
	Somnolence	Common
	Tremor	Common
Psychiatric disorders	Agitation	Common
	Insomnia	Very common

Note: The following preferred terms were combined: Administration site pain, Administration site reaction, Injection site induration, Injection site nodule, Injection site pain, and Injection site pruritus

combined into Injection Site Reactions and Sedation and Somnolence combined into Somnolence
Note: The adverse events were coded using the MedDRA version 12.0
[a] The frequency category is based on all subjects who received at least 1 dose of paliperidone palmitate in these studies (N=3817), where 'very common' is a frequency ≥1/10 and 'common' is a frequency ≥1/100 (CIOMS 1999).
rlst_adr_ge2perc_t1.rtf generated by rlst_adr_ge2perc.sas.

ADR terms that occurred in less than 2% of subjects treated with paliperidone palmitate in the key studies were the following:

- **Cardiac disorders:** atrioventricular block first degree, bradycardia, conduction disorder, palpitations, postural orthostatic tachycardia syndrome, sinus tachycardia
- **Ear and labyrinth disorders:** vertigo
- **Endocrine disorders:** hyperprolactinaemia
- **Eye disorders:** eye movement disorder, eye rolling, oculogyric crisis, vision blurred
- **Gastrointestinal disorders:** abdominal discomfort/abdominal pain upper, dry mouth, salivary hypersecretion, toothache
- **General disorders and administration site conditions:** asthenia, fatigue
- **Immune system disorders:** hypersensitivity
- **Investigations:** blood cholesterol increased, blood glucose increased, blood triglycerides increased, electrocardiogram QT prolonged, electrocardiogram abnormal
- **Metabolism and nutrition disorders:** decreased appetite, hyperglycaemia, hyperinsulinaemia, increased appetite
- **Musculoskeletal and connective tissue disorders:** back pain, joint stiffness, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, musculoskeletal stiffness, myalgia, nuchal rigidity, pain in extremity
- **Nervous system disorders:** bradykinesia, cerebrovascular accident, convulsion, dizziness postural, drooling, dysarthria, dyskinesia, dystonia, extrapyramidal disorder, hypertonia, lethargy, neuroleptic malignant syndrome, oromandibular dystonia, parkinsonism, psychomotor hyperactivity, syncope, tardive dyskinesia
- **Psychiatric disorders:** nightmare, restlessness
- **Reproductive system and breast disorders:** amenorrhoea, breast discharge, erectile dysfunction, galactorrhoea, gynaecomastia, menstrual disorder, menstruation delayed, menstruation irregular, sexual dysfunction
- **Skin and subcutaneous tissue disorders:** drug eruption, pruritis, pruritus generalized, rash, urticaria
- **Vascular disorders:** hypertension, orthostatic hypotension

Serious adverse event/deaths/other significant events

Table 35 lists all on study deaths, except for one death in study PSY-3005, which was due to aspiration of stomach contents before receiving any study drug, and the three post-study deaths of subjects receiving paliperidone palmitate.

Table 35. Deaths reported in completed studies with paliperidone palmitate

Subject Number (Study)	Age Sex	Dictionary-derived Term Reported Term	Day of Onset[a]	Protocol Phase	Onset Dose[b]	Invest. Relationship
Phase 2/3 Studies and the Long-Term Safety Study PSY-1008						
Placebo (total number of subjects, N=713)[c]						
650023 (R092670-PSY-3004)	66 Male	Pancreatic carcinoma pancreatic cancer	66	DB	<0>	Doubtful
Treatment Group: R092670 (total number of subjects in Phase 2/3 studies and Study PSY-1008, N=3817)						
604021 (R092670-PSY-3001)	53 Female	Completed suicide suicide	220	MA	<100>	Not related
604062 (R092670-PSY-3001)	56 Female	Accident fall out of window	135	MA	<100>	Not related
605026 (R092670-PSY-3001)	61 Male	Death death (natural causes, most likely from a stroke)	214	MA	<100>	Not related
618030 (R092670-PSY-3002)	56 Male	Acute myocardial infarction acute myocardial infarction	99	DB	<100>	Not related
690052 (R092670-PSY-3002)	25 Female	Death death (cause unknown)	196	DB	<0>	Not related
690096 (R092670-PSY-3002)	46 Female	Aspiration food aspiration	49	DB	<75>	Doubtful
630094 (R092670-PSY-3004)	48 Male	Completed suicide death due to suicide attempt	58	DB	<100>	Doubtful
604006 (R092670-PSY-3005)	25 Male	Completed suicide Suicide	81	DB	100	Not related
601732 (R092670-PSY-3006)	42 Male	Completed suicide Suicide	68	DB	<50>	Doubtful
603613 (R092670-PSY-3006)	53 Female	Death death (cause unknown)	1	DB	150	Not related
040712 (R092670-PSY-3007)	46 Female	Cerebrovascular accident brain stroke	13	DB	<150>	Doubtful
RISPERDAL CONSTA (total number of subjects, N=1199)						
690013 (R092670-PSY-3002)	53 Male	Carcinoid tumour pulmonary Pulmonary carcinoid tumor	135	DB	<50>	Not related
300278 (R092670-PSY-3008)	21 Female	Completed suicide Suicide	62	OL	<37.5>	Doubtful
Phase 1 Studies						
R092670 (total number of subjects in 10 Phase 1 studies, N=730)						
101015 (R092670-PSY-1002)	46 Male	Arrhythmia Cardiac arrhythmia	239	Period 2	<50>	Not related

A total of 12 on-study deaths have been reported in subjects treated with paliperidone palmitate (11 deaths in the 9 Phase 2/3 studies and study PSY-1008 and 1 death in the 10 other Phase 1 studies. One additional on-study death was reported in a subject who was randomly assigned to treatment but died before receiving any injections of the study drug in Study PSY-3005. Three post-study deaths in subjects treated with paliperidone palmitate were recorded, including 2 cases in study PSY-3001 and one in Study PSY-3004 (not included in Table 27). There was 1 death among subjects who received placebo and 2 on-study deaths among subjects treated with Risperdal consta. One post-study death was reported in a subject who received Risperdal consta in study PSY-3006.

There were no deaths in studies PSY-3003, SCH-201, PSY-1008, or in the double-blind recurrence prevention phase or the open-label extension phase of PSY-3001.

The occurrence of serious treatment-emergent adverse events was similar or slightly lower in the paliperidone palmitate group (5% to 13%) than in the placebo group (7% to 18%) across placebo-controlled double-blind studies. Across the Phase 2/3 studies and study PSY-1008, treatment-emergent serious adverse events other than psychiatric disorders were reported in isolated cases only. There was a slightly higher rate in serious adverse events in studies PSY-3002 and PSY-3006 for

paliperidone palmitate treatment compared to Risperdal consta treatment (29% versus 22% and 6.8% versus 4.8%). There was a higher incidence of serious psychiatric disorders in the paliperidonepalmitate group compared to the Risperdal consta group (PSY-3002: 25% vs. 20%; PSY-3006: 6.6% versus 4.1%) in these two studies. Psychiatric disorders as serious adverse events were among the most frequent reason for discontinuation of paliperidone palmitate therapy.

Laboratory findings

Paliperidone palmitate caused a slight increase in fasting insulin levels from baseline to endpoint. The overall increase in fasting insulin levels was more pronounced in Risperdal consta-treated subjects. In study PSY-3002, plasma fasting insulin levels were elevated by a mean (SD) of 11.6 (157.38) pmol/L relative to a baseline of 120.1 (124.37) pmol/L for paliperidone palmitate-treated subjects, and by a mean (SD) of 15.2 (151.45) pmol/L relative to a baseline of 110.7 (104.76) pmol/L for Risperdal Consta-treated subjects. Elevations in mean insulin levels were evident by Day 176 for paliperidone palmitate subjects and by Day 36 for Risperdal Consta subjects. In study PSY-3006, a mean increase of 7.4 pmol/L for fasting insulin levels was observed in the paliperidone palmitate group as compared to 18.1 pmol/L in the Risperdal Consta group. This is a well known effect of atypical antipsychotics.

Mean platelet counts decreases were observed in the paliperidone palmitate groups, whereas none could be detected in the placebo groups. In study PSY-3001, a small mean [SD] reduction from open-label baseline (-6.7 [46.13] giga/l to -16.8 [45.40] giga/l across treatment groups) and a slightly larger reduction from transition baseline (-20.5 [47.53] giga/l to –28.4 [45.64] giga/l across treatment groups) in mean platelet counts was observed at endpoint. In study PSY-1008, decreases in platelet count values of >25% from baseline were recorded for 20 subjects (11%) on Treatment A, and 3 subjects (12%) on Treatment B. Nonetheless, no unexpected adverse events with paliperidone palmitate suggestive of thrombocytopenia or bleeding-related adverse events were reported in the clinical studies.

The incidence of elevated prolactin concentrations was higher in the paliperidone palmitate groups for subjects of both gender (higher in females than in males) compared to the placebo group with a dose-related pattern in pooled studies PSY-3003, PSY-3004 but not in study PSY-3007. Studies PSY-3006, -3008 and -3002 revealed similar mean increases of prolactin concentrations in the paliperidone palmitate and the Risperdal consta groups. Observed increases in serum prolactin concentrations were mostly asymptomatic and infrequently associated with reported adverse events in controlled phase 2/3 studies.

The vital sign abnormality with the highest frequency observed throughout studies was standing pulse rates of ≥100 bpm with an increase of ≥15 bpm. Study PSY-1008 revealed the highest percentage of vital sign abnormalities, resulting from intensive vital sign measurement during the study.

Mean body weight and mean BMI increased from baseline to endpoint in a dose-dependent manner across most of the studies. Abnormal increase in body weight of 7% or above was detected in a higher percentage of subjects treated with paliperidone palmitate during long-term exposure (study PSY-1008, 27%; long-term relapse prevention study PSY-3001, 23%) due to intensive monitoring, whereas occurrence across all other studies was from 6-16%.

Other safety findings

Extrapyramidal symptoms (EPS)

The overall incidence of EPS-related adverse events in studies PSY-3003, PSY-3004, and PSY-3007 was similar for the placebo and paliperidone palmitate treatment groups (10% to 12%), except for the paliperidone palmitate 150 mg eq. group for which the incidence was higher (20%). There were 6 reports of tardive dyskinesia of the subjects treated with paliperidone palmitate in the 9 phase 2/3 studies and study PSY-1008: four subjects had a previous history of EPS and/or a previous long-term use of antipsychotics; two other cases of tardive dyskinesia – one in either study PSY-3001 and PSY-1008 – could be possibly related to the study drug. One mild but persisting case was also reported within the Risperdal Consta group.

In study PSY-1008, 24% of subjects who received paliperidone palmitate at doses up to 150 mg eq. reported EPS-related adverse events, most of which were of mild severity. The most common EPS-related adverse events were akathisia (9%), tremor (5%), parkinsonism (3%), and dystonia (2%). Four subjects experienced EPS-related serious adverse events of akathisia, parkinsonism, muscle rigidity, tremor, and/or dystonia, and 4 subjects were discontinued due to restlessness, muscle rigidity, musculoskeletal stiffness, and/or tremor. In study PSY-3005, the incidence of treatment-emergent EPS-related adverse events was similar across doses and was not markedly different between injection sites (gluteus, 8%; deltoid, 5%). In studies PSY-3002, PSY-3006, and PSY-3008, the incidences of most treatment-emergent EPS-related adverse events were similar between the paliperidone palmitate and Risperdal consta groups. Long-term studies with paliperidone palmitate revealed no increased risk of EPS compared to oral paliperidone (Invega). EPS-related adverse reactions were reported at rates of 7% to 20% in the 6-week, double-blind, placebo-controlled studies with Invega.

Neuroleptic malignant syndrome (NMS)

There was a single reported event of NMS among the paliperidone palmitate-treated subjects in the Phase 2/3 studies and study PSY-1008. This event presented on Day 15 following 2 injections of paliperidone palmitate 50 mg eq. in study PSY-3002, and was accompanied by elevated creatine kinase and increased liver enzymes. The investigator assessed the event as mild, and there was no documented evidence of admission to an intensive care unit or treatment with a muscle relaxant. The Applicant's assessment was that drug causality was possible but confounded by the presence of the LAI antipsychotic flupenthixol, which was discontinued 22 days before study drug administration.

Suicidality

Suicidality-related adverse events (completed suicide, suicidal behaviour, suicide attempt) occurred at a slightly higher incidence during study PSY-3003 and PSY-3004 compared to placebo (14 subjects versus 9 subjects). Suicidal ideation appeared in slightly higher rates in the paliperidone palmitate groups compared to Risperdal Consta during studies PSY-3002 and PSY-3006.

Seizures

Seizure-related adverse events were reported at incidences below 1% across studies, which is consistent with clinical and nonclinical data for risperidone.

Cardiovascular related adverse events

There was no notable difference between paliperidone palmitate and placebo, consistent with the findings for oral paliperidone (Invega) concerning occurrence of cardiovascular related adverse events (including severe cardiac arrhythmias and ischemia-related events). The incidence of these events did not appear to increase with longer exposure to paliperidone palmitate.

Cerebrovascular events in subjects treated with paliperidone palmitate included 2 confirmed reports of cerebrovascular accident, one of which resulted in death, and 1 case of cerebral infarction. In an additional case, the death of the subject was attributed by the investigator to "natural causes - most likely from stroke," although no clinical evidence was found. In each of these cases, the subjects had pre-existing risk factors for stroke. There were no reports of the adverse event term "sudden death," and no cases of ventricular tachycardia, ventricular fibrillation, ventricular flutter, or torsades de pointes among subjects treated with paliperidone palmitate.

Treatment-emergent abnormal ECG parameters (PR, QRS, and QT intervals) were observed at incidences not exceeding 2% in paliperidone palmitate-treated subjects. The frequency of "abnormal and clinically significant" ECG interpretation at endpoint was low in the pooled studies PSY-3003 and -3004 dataset (7% to 10% for paliperidone palmitate versus. 10% for placebo), in study PSY-3007 (7% across paliperidone palmitate dose groups versus. 4% in the placebo group), and in study PSY-3002 (9% for paliperidone palmitate versus. 7% for RISPERDAL CONSTA). Overall, paliperidone palmitate treatment was not associated with an increased risk of clinically significant ECG abnormalities.

Orthostatic hypotension

In the Phase 2/3 studies, treatment-emergent adverse events of orthostatic hypotension were uncommon. None of these events was severe, serious, or led to discontinuation of study treatment in paliperidone palmitate-treated subjects. These findings were consistent with the observations based on orthostatic changes in blood pressure and pulse rate, the incidence of orthostatic hypotension being ≤2% in either paliperidone palmitate or placebo groups. In study PSY-1008, mostly mild orthostatic hypotension was reported for 8.5% of the subjects, no cases of which were serious or led to discontinuation of treatment. Higher reported rates of orthostatic hypotension in study PSY-1008 were likely associated with the more frequent vital sign measurements during the course of this study, compared to the Phase 2/3 studies. In study PSY-3001, among paliperidone palmitate-treated subjects, the incidence of orthostatic hypotension during the open-label transition/maintenance and extension phases (1% for both) was similar to that during the double-blind phase. In study PSY-3005, rates of orthostatic changes were similar between injection sites (5% for deltoid, 4% for gluteus). In study PSY-3002, the rate of orthostatic changes in blood pressure and pulse rate was comparable for paliperidone palmitate and Risperdal consta groups (3% each). In studies PSY-3006 and -3008, orthostatic hypotension or syncope was reported by only 1 subject in each treatment group.

Weight gain

Mean body weight (actual values and percent changes) and mean BMI increased from baseline to end point in each of the paliperidone palmitate groups across studies and in each of the Risperdal consta groups in the comparator studies. In study PSY-1008, mean body weight and mean BMI increased from baseline to end point by 2.5 kg and 0.9 kg/m2, respectively, in subjects receiving long-term treatment with paliperidone palmitate at doses up to 150 mg eq. The mean percent change in body weight from baseline to end point was 3.9%. Clinically significant (≥7%) increases in body weight at end point were reported for 27% of the subjects.

Local injection site reactions

Although paliperidone palmitate injections were typically more painful than placebo, general local injection site tolerability was good in all Phase 2/3 studies and study PSY-1008.

In the pooled studies PSY-3003 and -3004, induration and swelling were observed at low rates for paliperidone palmitate and placebo (both 1%) and were generally mild. In study PSY-3007, in which a higher initiation dose was administered in the deltoid, the frequency of injection site pain was higher in the paliperidone palmitate groups (8% overall, with no dose-related trend) than with placebo (4%). In study PSY-3005, which compared the tolerability of deltoid and gluteal injection sites, symptom scores for the residual injection site were similar between deltoid and gluteal sites of administration. Switching between injection sites, regardless of the direction (ie, deltoid to gluteus or vice versa) was well tolerated.
In study PSY-1008, the overall tolerability of multiple injections of paliperidone palmitate 150 mg eq. in the long-term, open-label safety study was good. Induration, swelling, and redness were observed in no more than 10% of subjects throughout the study. Investigators reported that 25% of subjects experienced pain at the start of the study and 14% experienced pain at endpoint. Injection site pain was generally classified as mild. Investigator-rated injection site pain was more frequent following deltoid compared to gluteal injections.

In study PSY-3002, injection site pain was the most commonly reported adverse event associated with drug administration and was reported at similar rates for paliperidone palmitate and Risperdal consta (3% versus 2%) in that study. In study PSY-3006, the incidence of injection site-related adverse events was higher for the paliperidone palmitate group than for the Risperdal consta group: injection site pain (5.1% versus. 0.8%); injection site induration (1.5% versis. 0.3%); and injection site swelling (1.0% versus. 0.2%). None of these events was serious or led to study discontinuation, and most were mild or moderate in severity. In study PSY-3008, the incidence of injection site-related adverse events was low for both treatment groups: injection site pain (2.6% vs. 0.4%); injection site induration (0.9% vs. 0%); and injection site swelling (1.7% vs. 0%). In studies PSY-3002, PSY-3006, and PSY-3008, rating scores for pain, redness, induration, and swelling at the injection site were generally similar for the paliperidone palmitate and Risperdal consta groups.

Safety in special populations

Subgroup analyses by gender and age revealed inconsistent results concerning the safety profile. Some studies suggested a higher overall adverse event rate in females compared to males. An age-related pattern could not be detected. The examination of differences in incidences between racial cohorts also showed inconsistent results. These may be related to the disproportionate distribution of subjects by race. Furthermore no conclusion could be drawn on the comparison of the safety profile between subjects from EU-sites versus subjects from non-EU-sites, since most of the study subjects were from non-EU-sites with the exception of study PSY-3002.

There were 14 pregnancies in subjects who received paliperidone palmitate across all clinical studies, 12 of which occurred in the Phase 3 studies; 4 subjects had normal deliveries, 5 had elective abortions, 2 had spontaneous abortions, and in the other cases no further information was available. Based on the available data, paliperidone palmitate should only be used during pregnancy after careful assessment of the benefit-to-risk profile.

Paliperidone palmitate has not been studied in the paediatric population and no safety data are available according to the waiver granted for all subsets of this population.

Safety related to drug-drug interactions and other interactions

No human metabolic drug-drug interaction studies (CYP-450 inhibition studies) have been conducted with paliperidone palmitate.

Discontinuation due to adverse events

The highest discontinuation rate was seen during long-term exposure in study PSY-1008 (12.7%). More subjects in Treatment B discontinued from the study due to adverse events as compared to subjects in Treatment A (19.2% versus 11.8%). In all other short-term and long-term phase 2/3 studies, discontinuation rates due to adverse events did not exceed 8% in any paliperidone palmitate dosing group. More subjects in the placebo group discontinued study SCH-201due to TEAE compared to subjects in the paliperidone palmitate group (10% vs. 2%). There was no clear dose related pattern of discontinuation due to adverse events, except for a slightly higher rate in the 150 mg eq. dosing groups across studies. Studies PSY-3002, PSY-3006, and PSY-3008 revealed higher incidences of psychiatric adverse events leading to discontinuation in the paliperidone palmitate groups compared to Risperdal consta groups. There was an overall similar pattern of discontinuation adverse events due to psychiatric disorders across all studies, which were consistent with the underlying disease.

Post marketing experience

No post-marketing data for paliperidone palmitate were initially submitted by the applicant. At the CHMP request, cumulative reviews of post-marketing spontaneous cases in the elderly population as well as cases related to injection site reactions were performed.

Local injection site reactions

Sixty four cases of administration site reactions were reported in the worldwide company safety database and relate to six countries. The reporting rate of injection site reactions for paliperidone palmitate was 4.6 per 1,000 person-years. Of these cases, 97% were non serious; 25% were associated with treatment discontinuation or treatment interruption. The reporting rate of injection site reactions with risperidone LAI during a comparable period after launch was 21 per 1,000 person years,. Only 27 cases involving paliperidone palmitate had been entered into the FDA AERS database cumulatively through the fourth quarter of 2009.

Elderly population

This cumulative review included both oral paliperidone (Invega) and paliperidone palmitate.

Ninety-six cases valid cases reporting 119 unique preferred terms during the use of paliperidone PR. Unlisted preferred terms that were reported 2 or more times included: confusional state, dyspnoea, abasia, anxiety, blood creatine phosphokinase increased, catatonia, drug administration error, fall, myocardial infarction, and restless legs syndrome. Six cases reported a fatal outcome.

Four cases were retrieved reporting 6 unique preferred terms and use of paliperidone palmitate. Unlisted preferred terms included Anxiety and Hostility. None of these reports reported fatalities, events suggestive of a cardiovascular event, or events suggestive of a cerebrovascular event. In 3 of the 4 cases, the patients received a dose lower than recommended in the Company Core Data Sheet.

2.6.1. Discussion on clinical safety

The safety database for paliperidone palmitate was considered extensive and did not reveal any new safety concern as compared to the safety profile of oral paliperidone (Invega) or risperidone with the exception of the local injection site reactions. This safety concern was also reported as preclinical finding. Injection site pain was the most common adverse event following treatment with im injection of paliperidone palmitate, which is to be expected considering the irritant effect of the compound. In study PSY-1008, 25% of the patients experienced pain at the beginning of the study and 14% at the end of the study, indicating increased tolerance to injection site pain over time. The im injection also induced induration and swelling at fairly low rates. There is no or very slight difference in local injection site reactions between deltoid and gluteal sites of administration and from this point of view, dose administration in both muscles could be supported. In study PSY-3006, the incidence of injection site-related adverse events was higher for the paliperidone palmitate group than for the Risperdal consta group: injection site pain (5.1% versus. 0.8 %); injection site induration (1.5% versus. 0.3 %); and injection site swelling (1.0% versus. 0.2%).

Many of the common treatment-emergent adverse events in the placebo-controlled double-blind studies occurred at similar rates among the paliperidone palmitate and placebo groups. A slightly higher incidence of adverse events was noted at the highest dose of 150 mg eq. compared to 50-100 mg eq. The low number of subjects treated with 150 mg eq. (n=30) in pooled studies PSY-3003 and PSY 3004) did not clearly contribute to the number of TEAEs in this dosing group. Discontinuation due to a lack of efficacy was reported to be higher in this group compared to any other dosing groups or placebo (43%). In study PSY-1008, the most frequently reported treatment-emergent adverse events (>10%), in subjects receiving only paliperidone palmitate 150 mg eq. for at least 1 year were nasopharyngitis (19.2%), tachycardia (19.2%), injection site pain (14.4%), headache (12.5%), insomnia (11.5%), and weight increased (10.6%).The most frequently reported adverse events in subjects who required dose adjustment included dystonia, asthenia, sluggishness, and orthostatic hypotension.

The most common adverse events in all treatment groups except for local injection site reactions were related to nervous system and psychiatric disorders which were reported at a higher incidence in the placebo group as compared to the paliperidone palmitate groups. Many of these events were assumed to be associated with the underlying psychotic disorder and no concerns were raised in this regard. With respect to very common TEAEs, headache and insomnia occurred at higher incidences in paliperidone palimtate-treated subjects compared to placebo. Adverse events such as tachycardia, gastrointestinal disorders, increased weight, akathisia, dizziness and agitation were also among commonly reported events, more frequently seen in paliperidone palimitate treated groups.

The incidences and types of serious adverse events reported in subjects treated with paliperidone palmitate in the 9 phase 2/3 clinical studies, study PSY-1008, and clinical pharmacoloy studies were consistent with those reported for oral paliperidone (Invega). Serious treatment-emergent adverse events occurred at similar or slightly lower rates in the paliperidone palmitate-treated subjects compared to placebo-treated subjects in the completed placebo-controlled Phase 3 studies. Most of the serious adverse events that resulted in discontinuation of paliperidone palmitate therapy were psychiatric disorders.

Overall, the CHMP considered that the safety profile of paliperidone palmitate did not raise any new concern with the exception of the local injection sites reactions and this is reflected accordingly in the SPC. However, the applicant was requested to further discuss the safety profile of the highest proposed dose of 150 mg paliperidone palmitate and provide further safety data for the elderly population.

Use of the highest dose of paliperidone 150 mg eq

The applicant referred to data from studies PSY-1008 and PSY-3008 to support the safety profile of the highest dose of 150 mg eq paliperidone palmitate. In study PSY-1008, the highest proposed dose of 150 mg paliperidone palmitate was administered to 212 subjects. Most (88%) of 212 subjects enrolled in the study were in treatment A (150 mg eq paliperidone palmitate). Twenty six out of 212 subjects switched to treatment B (flexible dosing 50-150 mg eq) , while 7 subjects of these 26 continued to receive paliperidone palmitate 150 mg eq. One hundred and fifty one subjects (71.2%) received 150 mg eq as both the 3rd and 4th injections. Reasons for switching were not available due to a lack of systematic data collection.The open-label comparator study PSY-3008 also evaluated 150 mg eq. paliperidone palmitate mainly as an initial dose on day 1, the second injection on day 8 was a dose of 100 mg. Only 7 subjects received 150 mg eq. dosing three times during the initial four injections. 46 subjects received 150 mg eq. dosing two times during the initial four injections. Study PSY-3007 revealed similar rates of TEAEs in all dosing groups (25 mg eq., 100 mg eq., 150 mg eq.) except for EPS-related events, prolactin concentration, weight increase, body mass index, and abnormal weight increase of 7% or more, which were dose-dependent and were highest in the 150 mg eq. dosing group. On the basis of the applicant's responses, the CHMP considered that the use of the highest dose of 150 mg paliperidone palmitate can be recommended, taking into account that the risks did not outweigh the benefit in the targeted population.

Elderly population

The paliperidone palmitate clinical studies included 63 elderly subjects (5 subjects received placebo, 38 subjects were on paliperidone palmitate and 20 subjects on Risperdal Consta). Electrocardiogram QT prolonged was detected with 3% in the paliperidone palmitate group versus 0% in the other groups and musculoskeletal and connective tissue disorders were only detected in the paliperidone palmitate group (18%). One cerebrovascular accident and one complex partial seizure were reported in the paliperidone palmitate group.

On the basis of the available data (including post-marketing experience), the CHMP considered acceptable that information derived from risperidone is reflected in the SPC in addition to a statement in section 4.2 that the efficacy and safety in elderly > 65 years have not been established. The CHMP noted the single cerebrovascular accident reported during clinical studies and considered that this issue should be closely monitored as post marketing surveillance and identified as important potential risk in the risk management plan. In this respect, the applicant proposed to perform a post-authorisation safety study of the risk of cardiovascular and cerebrovascular events in elderly patients, including those with dementia, treated with paliperidone palmitate. A protocol outline has been provided as part of the risk management plan and final protocol is intended to be submitted as part of a follow up measure.

Local injection sites reactions

The CHMP agreed to convene CNS SAG to discuss the risk of reduced compliance and potentially increased risk for relapse/recurrence associated with the local adverse events.

The CNS SAG was held on 13 July 2010 and the main conclusions were the following:

- Follow-up data on implications for compliance are needed, and further clarification of the pathological nature of the local adverse reactions is necessary. Additional information is needed about post-marketing data related to local adverse reactions.

Based on the SAG recommendations, the applicant provided additional information as summarised below:

- Based on the blinded categorical ratings by the investigator, scores for pain, redness, induration, and swelling at the injection site were generally similar for paliperidone palmitate and Risperdal consta in the comparator studies.
- The ratings of injection site pain as measured by subjective Visual Analog Scale (VAS) indicate that the paliperidone palmitate injections were slightly more painful than placebo. Subject evaluations of injection site pain based on the VAS tended to lessen in frequency and intensity over time in all Phase 2 and 3 studies. As expected, injection into the deltoid were slightly more painful than corresponding gluteal injections. Over time, however, VAS ratings for injections in both the deltoid and gluteus decrease to the same extent.
- In comparison with Risperdal consta, mean subject evaluations of injection site pain based on the VAS over time were very similar.
- Across studies, local injection site reactions reported as adverse events, with isolated exceptions, were non-serious, generally mild to moderate in intensity, and were associated with a very low incidence of discontinuation. Reports of induration and nodule and mass formation were isolated and showed a similar pattern between paliperidone palmitate groups as compared to placebo and Risperdal consta. Based on adverse event reporting and outcomes, the local injection site reactions are unlikely to confer any increased risk of relapse due to withdrawal from treatment.
- Evaluation of local injection tolerability across paliperidone palmitate formulations with different particle sizes did not yield any evidence of clinically significant differences in the incidence of treatment-emergent adverse events in 142 subjects in Study PSY-1002.
- Based on the evaluation of post-marketing cases, injection site reactions with paliperidone palmitate are reported rarely, and the reporting rate for paliperidone palmitate (4.6 per 1,000 person-years) is lower compared with that observed for a similar period after launch for risperidone LAI (21 per 1000 patient years). Of the 64 cases retrieved for paliperidone palmitate, the vast majority was non serious, and 25% were associated with treatment discontinuation or interruption. Disproportionality analysis of cases in the FDA AERS and SRS databases yielded inconclusive results for the injection site reactions associated with paliperidone palmitate compared to other i.m. injectable antipsychotics marketed in the US. Due to the limitations inherent to spontaneous postmarketing adverse event reports, no definitive conclusion can be made regarding injection site reactions and compliance with paliperidone palmitate therapy**.**

On the basis of the applicant's responses, the CHMP considered that a reduced compliance with study medication or an increased risk of relapse or recurrence cannot be completely ruled out considering the increased number of reported adverse events related to injection site reactions compared to either placebo or Risperdal consta. This conclusion could also be drawn from the available post-marketing data in six countries. The applicant was asked to elaborate on how the risk of reduced compliance to study medication can be minimised. Sections 4.2 and 4.8 of the SPC were consequently updated to reflect on possible switch of injection site and detailed description of the adverse reactions. Information in the Package Leaflet was also included accordingly.

2.6.2. Conclusions on the clinical safety

Based on the data collected to date, the safety profile of paliperidone palmitate appeared favourable and similar with that of oral risperidone. Adequate information has been included in the SPC

concerning the injection site reactions. From the safety database, all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.7. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system has deficiencies that should be addressed as part of a follow up measure, these deficiencies (outstanding information on timelines for the flow chart and frequencies of the internal audits) do not prevent the granting of the marketing authorisation.

Risk Management Plan

The applicant submitted a risk management plan.

Table 36 Summary of the risk management plan.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important identified risks:		
• Prolactin-related adverse events	Routine pharmacovigilance as outlined in the RMP.	Labelling as outlined in Section 4.8 of the paliperidone palmitate SPC where hyperprolactinaemia and potentially prolactin-related adverse events (eg, amenorrhoea, galactorrhoea, gynaecomastia) are identified as ADRs.
• Increase in QT_cLD	Routine pharmacovigilance as outlined in the RMP.	The paliperidone palmitate SmPC identifies QT prolongation as a special warning/precaution (Section 4.4) and states that caution should be exercised in patients with known cardiovascular disease or family history of QT prolongation or in concomitant use with other medicines thought to prolong the QT interval. Caution is advised when prescribing paliperidone palmitate with medicines known to prolong the QT interval (Section 4.5). Electrocardiogram QT prolongation is listed as an ADR with paliperidone palmitate, INVEGA, risperidone, and other drugs in the antipsychotic class (Section 4.8) and is identified as a risk from overdose (Section 4.9)
• Orthostatic hypotension	Routine pharmacovigilance as outlined in the RMP.	The paliperidone palmitate SPC identifies Orthostatic hypotension as a special warning/precaution (Section 4.4), stating that paliperidone may induce orthostatic hypotension in some patients based on its α-blocking activity. Paliperidone palmitate should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions that predispose the patient to hypotension. The potential for an additive effect on orthostatic hypotension when paliperidone palmitate is administered with other therapeutic agents that have this potential is also stated (Section 4.5). Orthostatic hypotension is identified as an ADR (Section 4.8).
• Extrapyramidal symptoms/Tardive dyskinesia	Routine pharmacovigilance as outlined in the RMP.	The paliperidone palmitate SmPC identifies Tardive dyskinesia as a special warning/precaution (Section 4.4) in the use of medicines with dopamine receptor antagonistic properties, and identifies patients with Parkinson's Disease or Dementia with Lewy Bodies at potentially increased risk for extrapyramidal symptoms. Extrapyramidal symptoms and tardive dyskinesia are listed as ADRs (Section 4.8). Extrapyramidal symptoms are also identified in overdose (Section 4.9).

• Neuroleptic malignant syndrome	Routine pharmacovigilance as outlined in the RMP.	The paliperidone palmitate SPC identifies Neuroleptic malignant syndrome as a special warning/precaution (Section 4.4), stating that all antipsychotics, including paliperidone palmitate, should be discontinued if a patient develops signs or symptoms indicative of NMS. Patients with Parkinson's Disease or Dementia with Lewy Bodies are also identified as being at a potentially increased risk of NMS. NMS is listed in as an ADR (Section 4.8).
• Hyperglycaemia and glucose-related adverse effect	Routine pharmacovigilance as outlined in the RMP.	The paliperidone palmitate SmPC identifies Hyperglycaemia as a special warning/precaution (Section 4.4), and states that rare cases of glucose-related ADRs have been reported in clinical trials with paliperidone palmitate. Appropriate monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus. Hyperglycaemia is listed as an ADR (Section 4.8).
• Weight gain	Routine pharmacovigilance as outlined in the RMP.	The paliperidone palmitate SPC identifies weight increased as an ADR, and Weight gain is noted as dose-related (Section 4.8).
• Seizures	Routine pharmacovigilance as outlined in the RMP.	The paliperidone palmitate SmPC identifies Seizures as a special warning/precaution (Section 4.4), and states that paliperidone palmitate should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Caution is advised if paliperidone palmitate is combined with other medicines known to lower the seizure threshold (Section 4.5). Convulsion is identified as an ADR and grand mal convulsion is identified as ADR reported for oral paliperidone (Section 4.8).
• Somnolence	Routine pharmacovigilance as outlined in the RMP.	The SPC states that paliperidone palmitate should be used with caution in combination with other centrally acting medicinal products (Section 4.5). Paliperidone can have minor or moderate influence on the ability to drive and use machines, and patients should be advised not to drive or operate machines until their individual susceptibility to paliperidone is known (Section 4.7). Somnolence is listed as an ADR (Section 4.8). Additionally, drowsiness and sedation are identified in Section 4.9 (Overdose).
• Priapism	Routine pharmacovigilance as outlined in the RMP.	The paliperidone palmitate SmPC identifies Priapism as a special warning/precaution, and states that medicines with α-adrenergic blocking effects have been reported to induce priapism (Section 4.4). Priapism is also identified as an ADR for oral paliperidone (Section 4.8).
• Injection site reactions	Routine pharmacovigilance as outlined in the RMP.	The paliperidone palmitate SPC identifies Injection site reactions as an ADR (Section4.8)
• Cerebrovascular accident	Proposed pharmacovigilance study. Routine pharmacovigilance as outlined in the RMP.	The paliperidone palmitate SmPC identifies Cerebrovascular accident as an ADR (Section 4.8).
Important potential risks:		

• Pituitary adenomas	Routine pharmacovigilance as outlined in the RMP. .	The potential risk of Pituitary adenomas is addressed in Section 5.3 (Preclinical Safety Data) of the paliperidone palmitate SPC.
• Endocrine pancreas tumours	Routine pharmacovigilance as outlined in the RMP.	The potential risk of Endocrine pancreas tumours is addressed in Section 5.3 (Preclinical Safety Data) of the paliperidone palmitate SmPC.
• Breast cancer	Routine pharmacovigilance as outlined in the RMP.	The potential risk of Breast cancer is addressed in Section 5.3 (Preclinical Safety Data) of the paliperidone palmitate SPC.
• Increased mortality in elderly patients with dementia	Routine pharmacovigilance as outlined in the RMP.	The potential risk of Increased mortality in elderly patients with dementia is addressed in Section 4.4 (Special Warnings and Precautions For Use) of the paliperidone palmitate SmPC.
• Cerebrovascular adverse events in elderly patients with dementia	Proposed pharmacovigilance study. Routine pharmacovigilance as outlined in the RMP.	The potential risk for Cerebrovascular adverse events in elderly patients with dementia is addressed in Section 4.4 (Special Warnings and Precautions For Use) of the paliperidone palmitate SPC.
• Increased sensitivity to antipsychotics in patients with Parkinson's disease or dementia with Lewy Bodies	Routine pharmacovigilance as outlined in the RMP	The increased risk of NMS and Increased sensitivity to antipsychotics in patients with Parkinson's disease or dementia with Lewy Bodies are addressed in Section 4.4 (Special Warnings and Precautions For Use) of the paliperidone palmitate SmPC.
• Cognitive and motor impairment	Routine pharmacovigilance as outlined in the RMP	The potential risk for Cognitive and motor impairment is addressed in multiple sections of the paliperidone palmitate SPC. Section 4.7 (Effects on Ability to Drive and Use Machines) of the paliperidone palmitate SmPC. Somnolence is listed as an ADR (Section 4.8). Additionally, drowsiness and sedation are identified in Section 4.9 (Overdose).
• Antiemetic effect	Routine pharmacovigilance as outlined in the RMP	The potential risk of an Antiemetic effect is addressed in Section 4.4 (Special Warnings and Precautions For Use) of the paliperidone palmitate SPC.
• Venous thromboembolism	Routine pharmacovigilance as outlined in the RMP	The potential risk of Venous thromboembolism (VTE) is addressed in Section 4.4 (Special Warnings and Precautions For Use) of the paliperidone palmitate SmPC. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with paliperidone palmitate and preventative measures undertaken.
• Body temperature dysregulation	Routine pharmacovigilance as outlined in the RMP	The paliperidone palmitate SPC identifies body temperature dysregulation as a special warning/precaution, and states that disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicinal products (Section 4.4). Care is advised when prescribing paliperidone palmitate to patients who will be experiencing conditions which may contribute to an elevation in core body temperature or being subject to dehydration.
• Leukopenia	Routine pharmacovigilance as outlined in the RMP	None
• Neutropenia	Routine pharmacovigilance as outlined in the RMP	None

• Agranulocytosis	Routine pharmacovigilance as outlined in the RMP	None
• Suicidality	Routine pharmacovigilance as outlined in the RMP	None
Important missing information:		
• Use in paediatric patients	Routine pharmacovigilance as outlined in the RMP	Safety has not been established in paediatric patients and this is appropriately indicated in Section 4.2 (Posology and Method of Administration) of the paliperidone palmitate SmPC.
Important missing information :		
• Use in elderly patients	Proposed pharmacovigilance study. Routine pharmacovigilance as outlined in the RMP.	Safety has not been established in elderly patients and this is appropriately indicated in Section 4.2 (Posology and Method of Administration) of the paliperidone palmitate SPC.
• Use in haemodialysis patients	Routine pharmacovigilance as outlined in the RMP	Safety has not been established in patients with renal impairment and this is appropriately indicated in Section 4.2 (Posology and Method of Administration) of the INVEGA SmPC.
• Use in pregnancy	Routine pharmacovigilance as outlined in the RMP	Safety has not been established in pregnancy and this is appropriately indicated in Section 4.6 (Pregnancy and Lactation) of the paliperidone palmitate SPC.
• Use in nursing mothers	Routine pharmacovigilance as outlined in the RMP	Safety has not been established in nursing mothers and this is appropriately indicated in Section 4.6 (Pregnancy and Lactation) of the paliperidone palmitate SmPC.
• Drug utilisation in patients with schizophrenia	Proposed pharmacovigilance study. Routine pharmacovigilance as outlined in the RMP.	As stated in the SPC, paliperidone palmitate is approved for the maintenance treatment of schizophrenia in patients stabilised with antipsychotic medicine. It may be initiated without prior stabilisation in patients with mild to moderate psychotic symptoms and with previous responsiveness to paliperidone or risperidone.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Invega (paliperidone) and Doribax (doripenem). The bridging report submitted by the applicant has been found acceptable.

2.8. Benefit-Risk Balance

Benefits

- Beneficial effects

Paliperidone palmitate was developed with the aim to achieve an injectable product that would provide fast attainment of plasma concentrations above a minimum concentration for efficacy (primarily measured by the mean change from baseline in PANSS total score), but remaining below a maximum concentration for safety. A reasonable dosing interval between injections, good local injection site

tolerability and ease of administration were also important factors that were taken into account. A monthly dosing interval was considered appropriate.

Clinical pharmacokinetic studies have demonstrated the slow release profile of paliperidone palmitate, with maximum concentrations of paliperidone reached within 12-16 days after administration. The apparent half-life of paliperidone has ranged from 25-49 days, reflecting the release rate, i.e. flip-flop pharmacokinetics. In pharmacokinetic models, both simulated and observed plasma concentration data showed that for paliperidone palmitate, plasma concentrations of paliperidone that appeared lower only during the first days of treatment in comparison with oral administration of Invega 6 mg/day were achieved with the proposed dosing regimen.

The efficacy of paliperidone palmitate has been studied in an extensive clinical programme, in which the dosing regimen was changed during the development course.

In phase II/III study SCH-201, doses of 50 and 100 mg of paliperidone palmitate were tested and demonstrated statistically significant difference over placebo with a change from baseline at day 64 in PANSS total score of -5.2 and -7.8, respectively.

In study PSY-3007, a new enhanced dosing regimen was introduced with 150 mg at day 1 followed by 25, 50, 100 or 150 mg eq paliperidone palmitate. In this study, significant short term effects were demonstrated over placebo for all doses on the PANSS total score analysis ($p=0.034$ for 25 mg eq, $p<0.001$ for both 50 and 100 mg eq), supported by results for secondary endpoints (changes from baseline in CGI-S, PSP scores and responder rates) for the two higher doses (100 mg and 150 mg). In addition, a clear dose response was observed.

In study PSY-3006 using the finally recommended enhanced dosing regimen of 150 mg eq at day 1 and 100 mg eq at day 8, non inferiority was demonstrated in this short term study in the PP and ITT analyses: 0.4 [-1.62-2.38] and 1.2 [-0.78-3.16], respectively . This was supported by the secondary analyses of change in PANSS total score over time, responder rates, change in PSP and CGI-S scores.

In study PSY-3001, placebo controlled relapse prevention study, maintenance of effect was demonstrated.

Despite the absence of an in vivo direct comparison with exposure to oral paliperidone, available data from clinical studies with paliperidone palmitate and oral paliperidone showed that the onset of efficacy for oral paliperidone was by day 4 and for paliperidone palmitate some days later by day 8. In addition, no statistical difference between paliperidone palmitate and Risperdal consta (requiring oral supplementation for the first 3 weeks) treatment groups were observed with regard to change from baseline in PANSS total score during the first 36 days of treatment, suggesting that oral supplementation was not required for paliperidone palmitate.

- Uncertainty in the knowledge about the beneficial effects.

In short term study PSY-3003 testing 50, 100, 150 mg eq (at day 1,8, 36 and 64), results were less compelling than study SCH-201. In this study, statistically significant result for the primary efficacy endpoint was obtained for the 100 mg dose only ($p=0.019$). A minimal effect on the PANSS total score was observed for the 150 mg dose (-5.5) together with high withdrawal rate due to lack of efficacy (43%).

In short term and long term studies PSY-3008 and -3002, non inferiority versus Risperdal consta could not be concluded.

No in vivo direct comparison with exposure to oral paliperidone was performed.

Uncertainties in the dosing recommendation for obese patients subject to lower exposure and poorer efficacy outcome were identified and have been requested to be adequately addressed in the SPC.

Risks

- Unfavourable effects

No new safety issues have been identified in preclinical studies conducted with paliperidone palmitate as compared to oral paliperidone or risperidone to the exception of local injection site reactions. These were also observed during clinical studies with a higher frequency versus placebo and Risperdal consta groups.

Study PSY-3007 revealed similar rates of TEAEs in all dosing groups (25 mg eq., 100 mg eq., 150 mg eq.) except for EPS-related events, prolactin concentration, weight increase, body mass index, and abnormal weight increase of 7% or more, which were dose-dependent and were highest in the 150 mg eq. dosing group.

Limited data on the elderly population (n=63) was available. One cerebrovascular accident in this population was reported during clinical studies.

- Uncertainty in the knowledge about the unfavourable effects.

A reduced compliance with study medication or an increased risk of relapse or recurrence cannot be completely ruled out considering the increased number of reported adverse events related to injection site reactions compared to either placebo or Risperdal consta.

Further data in elderly patients are intended to be collected via a post-authorisation safety study of the risk of cardiovascular and cerebrovascular events in elderly patients, including those with dementia, treated with paliperidone palmitate. This is part of the risk management plan.

A drug utilisation study to assess the usage of paliperidone palmitate in the approved indication (schizophrenia) in Europe is also intended to be performed as part of the risk management plan.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

The effects demonstrated versus placebo as well as the active comparator Risperdal Consta were considered clinically relevant. No need for initial oral coverage and the prolonged dosing interval (one month) were considered to be of particular benefit. Besides, the possibility to administer paliperidone palmitate without prior stabilisation on oral treatment in selected patients with mild to moderate symptoms and with prior established responsiveness to paliperidone or risperidone was also considered of important added value.

The only new safety issues as compared to oral paliperidone of importance were the injection site reactions. Although these might affect the adherence to treatment they were considered to be manageable with routine pharmacovigilance and adequate labelling.

- Benefit-risk balance

Having considered the benefits of this new depot formulation (paliperidone palmitate) over the limited new risks identified as compared to the oral formulation (paliperidone), already approved in the treatment of schizophrenia, the CHMP concluded that the benefit risk balance for Xeplion is positive for the following indication:

"XEPLION is indicated for maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone.

In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, XEPLION may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed."

Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

Phamacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

No additional risk minimisation activities were required beyond those included in the product information.

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Xeplion in the "maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone. In selected patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, Xeplion may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed." was favourable and therefore recommended the granting of the marketing authorisation.